EVALUATION OF PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH OTHER MICROVASCULAR COMPLICATIONS

Dissertation submitted in partial fulfillment of regulation for the award of M.D. Degree in General Medicine (Branch I)

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CERTIFICATE

Certified that this is the bonafide dissertation done by ***DR NEETHA BALARAM*** *and submitted in partial fulfillment of the requirements for the Degree of M.D., General Medicine, Branch I of The Tamilnadu Dr. M.G.R. Medical University, Chennai.*

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DECLARATION

I solemnly declare that the dissertation titled **"EVALUATION OF PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH OTHER MICROVASCULAR COMPLICATIONS"** was done by me from September 2009 to September 2010 under the guidance and supervision of **Professor Dr.K..Govindarajan M.D., DM.**

This dissertation is submitted to the Tamilnadu Dr. MGR Medical University towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

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Introduction

INTRODUCTION

Diabetes Mellitus is a common and a serious disease with chronic complications and constitutes a substantial burden for both patient and health care system. In 2010, the global prevalence of diabetes was estimated at 285 million, corresponding to 6.4% of world's adult population. This figure is predicted to reach 438 million by 2030 as a consequence of longer life expectancy, sedentary life style and changing dietary patterns. According to recent estimates, presently India has 32 million diabetic subjects, and this is projected to increase to 100million i.e. rise by 250% by the year 2035. In the CUPS (Chennai urban population) study by Mohan et al, 12% of individuals above age of 20 years in Chennai were found to be diabetic in the year 1997. In the more recent CURES study, conducted on 26,001 individuals showed that 16% now have diabetes in Chennai. [1,2,3]

Vascular complications both micro and macrovascular predominate the features of Indian diabetes due to delayed diagnosis. Various microvascular complications in diabetes mellitus includes

• Diabetic Retinopathy

• Diabetic Nephropathy

• Diabetic Neuropathy

Presence of microvascular complications at the time of diagnosis of diabetes mellitus are showing increasing trend in India. Early detection of microvascular complications and its treatment at this time by intensive therapy can prevent progression of these complications and hence morbidity and mortality among patients.

Diabetic Neuropathy is one of the most common troublesome complications of diabetes mellitus. The prevalence of neuropathy is related to age, duration of diabetes and the quality of metabolic control, by the time a diabetic patient has severe neuropathy, retinopathy and albuminuria are also usually present. Diabetic neuropathy is clinically present in 30-50% of all diabetes patients. Diabetic foot accounts for one of the largest inpatients admissions in India.[4,5]

The primary pathological role of hyperglycemia in diabetic complications is well established. With the increasing knowledge that maintenance of euglycemia greatly reduces, if not prevents the risk of diabetic complications and at times helps even in regression of such complications, monitoring the control of diabetes is essential for the successful management of the diabetes[6].

Keontg and Gabbay and their co-workers have suggested measurement of glycosylated hemoglobin (HbA1C) as an indicator of diabetic control. HbA1C is formed by the post-transcriptional

glycosylation of HbA at the amino-terminal valine of Beta chain. When properly assayed HbA1C level in a blood sample gives an estimate of diabetic control for preceding 3-4 month period (i.e. life span of RBC)[7,8]. DCCT study proved that a glycated Hemoglobin (HbA1C) reduction from 9 to 7% for a mean follow up of 6.5 years was able both to reduce the onset of diabetic neuropathy (from 9.6% 2.8%) and to slow its progression. However, euglycemia is only able to halt the progression, rather than reverse it, once the nerve damage is established.[9,10]

The relative effect of cardiovascular risk factors specifically associated with diabetes (e.g., hypertension, dyslipidemia, and increased weight) or not associated with diabetes (smoking) on the development of neuropathy are incompletely elucidated. The Diabetes Control and Complications Trial (DCCT) reported a 60 percent reduction in neuropathy in the intensively treated groups after five years but the cumulative incidence of neuropathy (15 to 21 percent) and abnormal nerve conduction (40 to 52 percent) remained substantial. Such findings suggest that neuropathy can develop, despite intensive control of the glucose level.Thus, risk factors besides hyperglycemia are probably involved in the evolution of neuropathy.[9,10] Identifying them, particularly if they are modifiable, might lead to new risk-reduction strategies. The European Diabetes (EURODIAB) Prospective Complications Study

aimed to define and assess the relative importance of other, potentially modifiable factors that increase the risk of distal symmetric neuropathy in patients with type 1 diabetes mellitus.

The present study aims to evaluate peripheral neuropathy in type 2 diabetes patients by clinical examination and electrophysiologicaly by nerve conduction studies and to correlate it with the other microvascular complications and various risk factors such as age, sex, duration of diabetes, HbA1C, body mass index, systemic hypertension and hypercholesterolemia. The importance of this study lies in the fact that the morbidity and mortality in diabetes is attributed to a large extend by its complications. Early detection and treatment of these complications therefore plays a crucial role. Other than glycemic control, there are no treatments for diabetic neuropathy. Thus, identifying potentially modifiable risk factors for neuropathy is crucial. Detecting these risk factors helps in correcting these at an early stage. Correlation between the various microvascular complications helps in better understanding of their pathogenesis and early control.

Aims & Objectives

AIMS AND OBJECTIVES

- To evaluate peripheral neuropathy in type 2 diabetes patients by clinical examination and electrophysiologicaly by nerve conduction study and thus do a comparative analysis.

- To study the correlation of diabetic peripheral neuropathy with other microvascular complications by assessing microalbuminuria and retinopathy.

- To study the correlation of diabetic peripheral neuropathy with age, sex, duration of diabetes, body mass index, systemic hypertension and total serum cholesterol.

Review of Literature

REVIEW OF LITERATURE

"To know diabetes is to know medicine"

Historic Review

Knowledge of diabetes dates back to Centuries before Christ. The Egyptian PAPYRUS EBCRS (Ca.1500 B.C) described an illness associated with the passage of much urine. First clear clinical description was given by CELSUS in the first century (30BC to 50 A.D).

The word "DIABETES" coined by ARETAEUS, of CAPPADOCIA probably derived from Greek work Indicating "Running Through as a Siphon". "because the fluid does not remain in the body but uses the man's body as a ladder whereby to leave it". The disease is better understood in India. CHARAKA (2^{nd} century AD) in his "Charaka Samhita" has mentioned the sweetness of urine in addition to the symptom of polyuria. The ancient Indian surgeon Sushruta (500 AD) described the disease as "Madhu Meha" (Honey Urine) with symptoms of polyphagia, polydypsia and polyuria. Avicenna (980–1037), an Arab Physician gave the first description of diabetic gangrene. FREDRICK-BANTING AND CHARLES BEST discovered insulin in 1922.

JOHN ROLLO IN 1978 recorded the involvement of Nervous system in diabetes. MARACHAL DE CALVI (1864) first suggested that diabetes might be the cause rather than the effect of Neuropathy.

PAVY (1885) gave a detailed description of the clinical manifestation of diabetic neuropathy. R.W. RUNNDLES wrote that entire nervous system may be involved including central, autonomic and peripheral systems, but more commonly peripheral system. JORDON (1936) AND RUDDLES (1945) gave the first clear description of autonomic neuropathy.

IN 1936, Jordon tried to classify the neurological manifestation into 3 groups.

1. Hyperglycemic symptoms-Reversed upon treatment.
2. Circulatory degenerative type
3. Neurotic type

THOMAS AND LESCELLES (1966) described an increased incidence of segmental demyclination in diabetic Neuropathy. BISHOP (1968) postulated that a disordered lipid metabolism in the Schwann cells results in demyelination. In monitoring the control of diabetes, estimation of urine sugar and blood sugar have drawback as it requires patient compliance and frequent measurements.

Consequently GABBAY et al, in 1976 suggested measurement of Glycosylated hemoglobin as an indicator of diabetic control [15,16]

Diabetes Mellitus

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action or both. The metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiological changes in multiple organ systems. With an increasing incidence world wide, diabetes mellitus will be the leading cause of morbidity and mortality in the future.

Etiologic classification of diabetes mellitus[17]

1. **Type 1 Diabetes** (β-cell destruction, usually leading to absolute insulin deficiency).
   A. Immune mediated
   B. Idiopathic

2. **Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance).

3. **Other specific types of diabetes**

A. Genetic defects of β-cell function characterized by mutation in:

- Hepatocyte Nuclear Transcription Factor (HNF) 4α (MODY 1)
- Glucokinase (MODY 2)
- HNF-1α (MODY 3)

- Insulin promoter factor (IPF) 1 (MODY 4)
- HNF-1β (MODY 5)
- Neuro D1 (MODY 6)
- Mitochondrial DNA
- Proinsulin or insulin conversion

Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson Mendenhall syndrome
4. Lipodystrophy syndromes

B. Diseases of the exocrine pancreas–pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy.

C. Endocrinopathies–acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma.

D. Drug or chemical induced–Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, beta – adrenergic agonists, thiazides, phenytoin, α-interferon, protease inhibitors, clozapine, β-blockers.

E. Infections – congenital rubella, cytomegalovirus, coxsackie.

F. Uncommon forms of immune mediated diabetes–"stiff-man" syndrome, anti-insulin receptor antibodies.

G. Other genetic syndromes sometimes associated with diabetes. Down's syndrome, Klinefelter's syndrome, Turner's syndrome, wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence Moon Biedl Syndrome, myotonic dystrophy, porphyria, Prader – Willi syndrome.

4. Gestational Diabetes

Diagnostic criteria for diabetes mellitus[17]

The criteria for diagnosis of diabetes are shown in the table:

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS
• Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)[a] or • Fastng plasma glucose ≥ 7.0 mol/L (126 mg/dL)[b] or • Two-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test [c]

Three ways to diagnose diabetes are possible and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day by any one of the 3 methods, given in the table. The use of the hemoglobin A1C (HbA1C) for the diagnosis of diabetes is not recommended at this time.

COMPLICATIONS OF DIABETES

Diabetes has both acute and long-term complications. They are :

Acute

- Diabetic ketoacidosis
- Hyperglycemic hyperosmolar state
- Hypoglycemia

Long term

- Retinopathy
- Neuropathy
- Nephropathy
- Ischemic heart disease
- Cerebrovascular disease
- Peripheral vascular disease

Others

- Infections
  - UTI

- Tuberculosis
- Candidiasis – Oral / Vulvovaginal
- Mucormycosis
- Necrotising fasciitis
- Periodontitis

Microvascular complications in Diabetes Mellitus

All forms of diabetes, both inherited and acquired, are characterized by hyperglycemia, a relative or absolute lack of insulin, and the development of diabetes specific microvascular pathology in the retina, renal glomerulus, and peripheral nerve.

Pathogenesis

Diabetes mellitus causes both microvascular and macrovascular complications. It has been showed in studies that microvascular complications are mainly because of hyperglycemia, whereas insulin resistance is the major determinant in macrovascular disease. Atherosclerosis is the pathological entity in macrovascular disease.

Microvascular complications are due to following mechanisms[18]

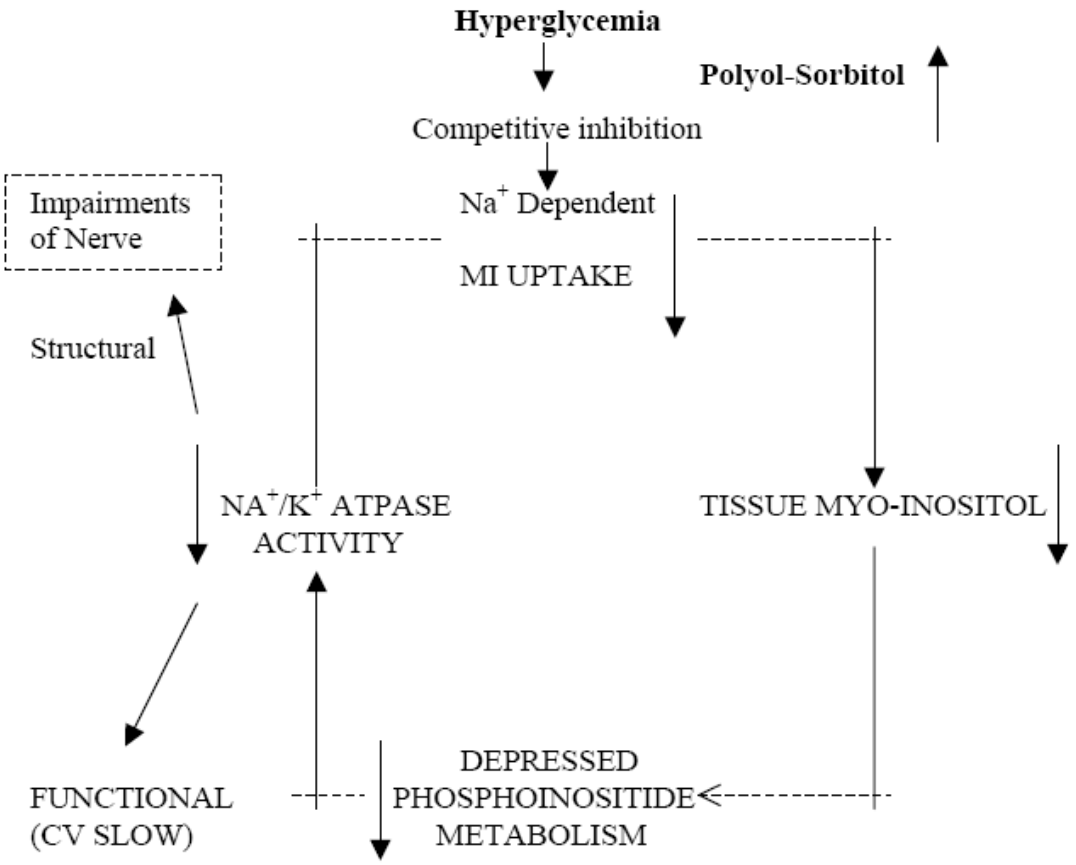
Most cells are able to reduce the transport of glucose inside the cell when they are exposed to hyperglycemia, so that their internal glucose concentration stays constant. In contrast, the cells damaged by hyperglycemia are those that cannot do this efficiently.

Thus, diabetes selectively damages cells, like endothelial cells and mesangial cells.

i. Myoinositol Metabolism

Glucose acts a virtually the sole source of energy in peripheral nerves as well as in the brain. It enters nerve cells through insulin – independent pathways and is used in the production of ATP. Although, ATP production does not appear impaired, experimental diabetic nerves do demonstrate a reduction in ATP utilization, thought to be secondary to decrease Na/K ATPase activity. Decreased Na/K ATPase activity has been shown to correlate to decreased myoinositol concentrations within peripheral nerves in diabetic animals.

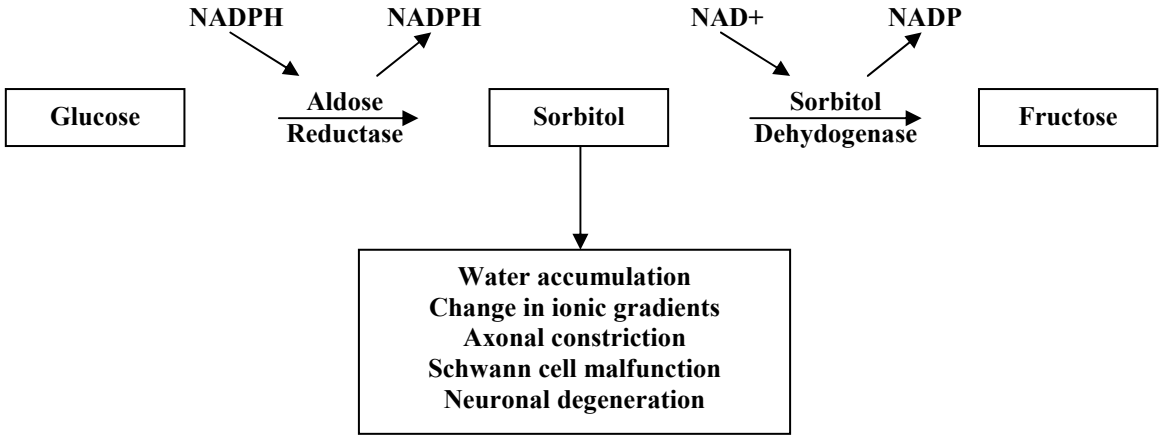
Myoinositol is a normal dietary hexose having structural similarity to glucose. It is an important constituent of phospholipid and cell membrane, is 90 to 100 times more concentrated in peripheral nerves than in plasma.



Hyperglycemia results in competitive inhibition of the sodium-dependent transport system responsible for myoinositol uptake. This decreased uptake is hypothesized to contribute to the decreased concentration of myo-inositol found in the peripheral nerve, as well as decreased Na/K ATPase activity. Na/K ATPase impairment not only results in decreased nerve cell membrane potential and, therefore decreased nerve conduction, but also decreased sodium dependent myo-inositol uptake creating a worsening cycle. Myo-inositol replacement restores the normal nerve function.

Increased flux through the polyol pathway

The polyol pathway focuses on the enzyme aldose reductase. Aldose reductase normally has the function of reducing toxic aldehydes in the cell to inactive alcohols, but when the glucose concentration in the cell becomes too high, aldose reductase also reduces that glucose to sorbitol, which is later oxidized to fructose. In the process of reducing high intracellular glucose to sorbitol, the aldose reductase consumes the cofactor NADPH. NADPH is also the essential cofactor for regenerating a critical intracellular antioxidant, reduced glutathione. By reducing the amount of reduced glutathione, the polyol pathway increases susceptibility to intracellular oxidative stress.



Intracellular production of advanced glycation endproducts (AGE)- It is harmful by three mechanisms

The first mechanism, is the modification of intracellular proteins including, most importantly, proteins involved in the regulation of gene transcription

1. Glycosylated nerve protein – alteration in myelin macrophage interaction – segmental demyelination.[35]
2. Glycosylated protein in RBC membrane – decreased RBC deformability and Gly. Serum protein – Hyperviscosity -- Tissue hypoxia – Nerve dysfunction.
3. Glycosylated Hemoglobin – greater affinity for oxygen – Tissue hypoxia – nerve dysfunction (Ditizel and Strandl, 1975).

Second mechanism, is that these AGE precursors can diffuse out of the cell and modify extracellular matrix molecules nearby, which changes signaling between the matrix and the cell and causing cellular dysfunction. . Advanced glycation end products have been shown to have an effect on matrix metalloproteinases, which might damage nerve fibers

The third mechanism is that these AGE precursors diffuse out of the cell and modify circulating proteins in the blood such as albumin. These modified circulating proteins can then bind to AGE receptors and activate them, thereby causing the production of inflammatory cytokines and growth factors, which in turn cause vascular pathology

Protein kinase activation (PKC activation)

Hyperglycemia inside the cell increases the synthesis of a molecule called diacylglycerol, which is a critical activating cofactor for the classic

isoforms of protein kinase. When PKC is activated by intracellular hyperglycemia, it has a variety of effects on gene expression. In each case, the things that are good for normal function are decreased and the things that are bad are increased. For example, the vasodilator producing endothelial nitric oxide (NO) synthase (eNOS) is decreased, while the vasoconstrictor endothelin-1 is increased.

Increased hexosamine pathway activity

Next mechanism is increased flux through the hexosamine pathway. When glucose is high inside a cell, most of that glucose is metabolized through glycolysis,going first to glucose-6 phosphate, then fructose-6 phosphate, and then on through the rest of the glycolytic pathway. However, some of that fructose-6-phosphate gets diverted into signaling pathway in which an enzyme called GFAT (glutamine fructose-6 phosphate amidotransferase) converts the fructose-6 phosphate to glucosamine-6 phosphate and finally to UDP (uridine diphosphate) *N*-acetyl glucosamine. The *N*-acetyl glucosamine gets put onto serine and threonine residues of transcription factors, just like the more familiar process of phosphorylation, and over modification by this glucosamine often results in pathologic changes in gene expression. For example, increased modification of the transcription factor Sp1 results in increased expression of transforming growth factor ß1 and plasminogen activator inhibitor-1, both of which are bad for diabetic blood vessels.

Hyperglycemia increases superoxide production by the mitochondria and causes oxidative stress on the cells

In diabetic cells with high glucose inside, there is more glucose being oxidized in the TCA cycle, which, in effect, pushes more electron donors (NADH and FADH2) into the electron transport chain. As a result of this, the voltage gradient across the mitochondrial membrane increases until a critical threshold is reached. At this point, electron transfer inside complex III is blocked, causing the electrons to back up to coenzyme Q, which donates the electrons one at a time to molecular oxygen, thereby generating superoxide.

Mitochondrial overproduction of superoxide activates the four major pathways of hyperglycemic damage by inhibiting GAPDH. This is the key pathway, which activates all other pathways thus unifying the mechanism.

Macrovascular Pathogenesis

For microvascular disease end points, there is a nearly 10-fold increase in risk as HbA1C increases from 5.5 to 9.5%. In contrast, over the same HbA1C range, macrovascular risk increases only about twofold. Hence hyperglycemia is not the major determinant of diabetic macrovascular disease.

Insulin resistance is the main pathophysiologic abnormality found in these patients. Insulin resistance causes mitochondrial overproduction of ROS in macrovascular endothelial cells by increasing FFA flux and oxidation. And, as hyperglycemia, this FFA-induced increase in ROS activates the same damaging pathways: AGEs, PKC and hexosamine pathway.

Diabetic neuropathy

General Consideration

Diabetic neuropathy is one of most common long-term, complications of diabetes mellitus and is clinically present in 30-50% of all diabetic patients. The clinical and electro-physiological evidence of diabetic peripheral neuropathy is estimated to be about 70% in both type-I and type II diabetes mellitus.

Distal symmetrical polyneuropathy (DSPN) is a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (diabetes) and cardiovascular risk covariates. The various risk factors were studied, which predispose to the early development of diabetic neuropathy. The most important-factor is the level of hyperglycemia. The fasting blood sugar is major determinant of neuropathy independent of diabetic duration, age and body mass index. The high Glycosylated

hemoglobin associated with increased incidence of distal symmetrical neuropathy (DSN) and DAN.Orskoy. L et al found that neuropathy only rarely developed in patients with Glycosylated hemoglobin below 7%.[19].

Classification[20,21]

Since mixed syndromes are frequent in diabetic neuropathy it is very difficult to classify the diabetic neuropathy as observed by many workers.

1. Bruyn and Garland Classification

I. Symmetrical, predominantly sensory, and distal polyneuropathy

A. Diabetic pseudotabes

B. Hyperalgesic type

II. Asymmetrical, predominantly motor, and often proximal neuropathy

A. Mononeuropathy

B. Multiple neuropathy

C. Autonomic visceral neuropathy

D. Radiculopathy

2. Thomas' Classification

I. Symmetrical polyneuropathies

A. Sensory or sensorimotor polyneuropathy

B. Acute or subacute motor neuropathy

C. Autonomic neuropathy

II. Focal and multifocal neuropathies

A. Cranial neuropathy

B. Trunk and limb mononeuropathy

C. Proximal motor neuropathy

3. Boluton and Ward Classification

I. Mononeuropathy

A. Cranial

B. Truncal

C. Multiple

II. Polyneuropathy

A. Acute sensory neuropathy

B. Chronic sensori motor

C. Autonomic

D. Proximal

E. Truncal motor

4. Classification by topography

Somatic Neuropathies

I. Distal Symmetric Diabetic Neuropathy

A. Predominantly sensory

- Small fibre (pain and temperature sensory function)

- Larger fibre (Propricoeptive, vibrational, and muscle reflex sensory function).
- Mixed large and small fibre

B. Predominantly motor

- With sensory neuropathy
- With hypoglycemia

II. Proximal Symmetric Diabetic Neuropathy

III. Asymmetric Diabetic Neuropathy

A. Predominantly sensory : Intercostal radiculopathy , Truncal radiculopathy

B. Predominantly Motor : Cranial neuropathy, Peripheral neuropathy{Median (Carpal's tunnel syndrome), ulnar, popliteal}

C. Proxmial neuropathy

IV. Autonomic Neuropathies

I. Cardiovascular

Exercise intolerance, Cardiac denervation syndrome. Orthostatic regulation

II. Gastrointestinal

Gastric emptying abnormalities, Constipation, Diabetic diarrhea, Incontinence

III. Genito-urinary

Bladder dysfunction, Sexual dysfunction

IV. Counter – Regulatory

V. Sudo Motor

EXAMINATION SCORES FOR DIABETIC NEUROPATHY[22]

Frequently used and accepted examination scores for diabetic neuropathy are the Neuropathy Disability Score (NDS) , the Neuropathy Impairment Score in the Lower Limbs (NISLL) , various modified NDS scores, the Neuropathy Deficit Score, the Michigan Neuropathy Screening Instrument (MNSI), and the Clinical Examination Score of Valk (CE-V).

The NDS was designed for neuropathy in general. Although the score is well founded and complete, it is difficult to perform in clinical practice on patients with diabetic foot problems. Precise descriptions of how the tests should be performed and how items should be scored are lacking. The NISLL is a modification of the NDS specific for distal PNP, although motor activity grading is the focus and involves 64 of a

maximum of 88 points . The NIS-LL and the Neuropathy Deficit Score has not been validated.Feldman et al. developed a combination of 2 scoring systems: the MNSI (symptom and examination score) and the Michigan Diabetic Neuropathy Score (neurological examination and nerve conduction studies). These scores do not have a separate examination score as advised by consensus reports. The CE-V can be used to examine sensory functions, tendon reflexes, and muscle strength in the lower extremities . The scoring systems of Feldman et al. and Valk et al.have been validated and are easy to perform in clinical practice. None of the aforementioned scores is known to be hierarchical.

The Symptom Score (DNS), and Examination Score (DNE), which were designed by Meijer, are simple, reproducible, fast and easy to perform and were modified from the widely used Neuropathy Symptom Score and Neuropathy Disability Score of Dyck.

Diabetic neuropathy symptom score

All subjects were questioned regarding the presence or otherwise of symptoms, either positive or negative suggesting the presence of neuropathy. The questionnaire was the Diabetic Neuropathy Symptom DNS Score adopted from the Neuropathy Symptom Score (NSS) of Dyck.

Diabetic neuropathy symptom Score: The questions should be answered ‘yes’ (positive: 1 point) if a symptom occurred more times a week during the last 2 weeks or ‘no’ (negative: No point) if it did not.

1. Symptoms of unsteadiness in walking?
2. Do you have a burning, aching pain or tenderness of your legs or feet?
3. Do you have pricking sensations at your legs and feet?
4. Do you have places of numbness on your legs or feet?

Maximum score: 4 points; 0 points- PNP absent; 1-4 points - PNP present

THE DIABETIC NEUROPATHY EXAMINATION (DNE) SCORE

The NDS, as the most complete and accepted score, was used for item selection to develop the DNE. The new instrument is the DNE, which is a scoring system with 8 items. It was validated in diabetic patients with a wide spectrum of complications. The DNE is hierarchical, sensitive, fast, and easy to perform in clinical practice (application takes 5 min).

Diabetic Neuropathy Examination

Muscle strength

1. Quadriceps femoris: extension of the knee
2. Tibialis anterior : dorsiflexion of the foot

Reflex

3. Triceps surae

Sensation: index finger

4. Sensitivity to pinpricks

Sensation: big toe

5. Sensitivity to pinpricks
6. Sensitivity to touch
7. Vibration perception
8. Sensitivity to joint position

Only the right leg and foot are tested.

Scoring from 0 to 2:

0 = Normal

1 = Mild/moderate deficit

- Muscle strength: Medical Research Council scale 3–4
- Reflex: decreased but present
- Sensation: decreased but present

2 = Severely disturbed/absent

- Muscle strength: Medical Research

  Council scale 0–2
- Reflex: absent
- Sensation: absent

  Maximum score: 16 points

A score of > 3 indicates presence of polyneuropathy.

Electrodiagnostic studies.[24]

No single reference standard defines distal symmetric polyneuropathy. The most accurate diagnosis of distal symmetric polyneuropathy comprises a combination of clinical symptoms, signs, and electrodiagnostic findings. Electrodiagnostic findings should be included as part of the case definition since they provide a higher level of specificity for the diagnosis.

Electrodiagnostic studies are sensitive, specific, and validated measures of the presence of polyneuropathy. Electrodiagnostic evaluations commonly include both nerve conduction studies (NCSs) and needle EMG. In the diagnosis of polyneuropathy, NCSs are the most informative part of the electrodiagnostic evaluation. NCSs are noninvasive, standardized, and provide a sensitive measure of the functional status of sensory and motor nerve fibers. NCSs are also widely performed and suitable for population studies or longitudinal evaluations.

The inclusion of NCSs in the assessment of polyneuropathy adds a higher level of specificity to the diagnosis.For these reasons, NCSs are included as an integral part of the case definition of polyneuropathy.

The protocol for performing NCSs was determined by a structured consensus process. There are many previous recommendations regarding NCS criteria for the diagnosis of polyneuropathy, but no formal consensus exists. The recommendations that follow are based on electrophysiologic principles that combine both the highest sensitivity and specificity as well as the highest efficiency for the diagnosis of distal symmetric polyneuropathy.

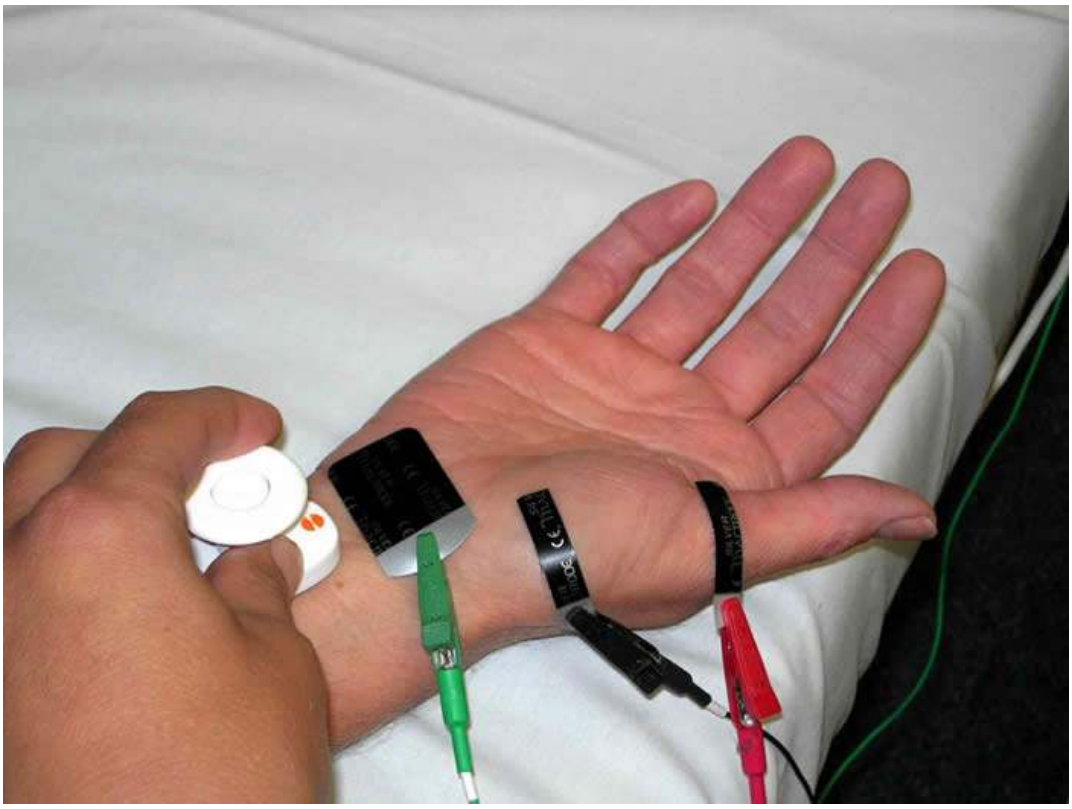
Technique of nerve conduction study[25]

NCS involve the application of a depolarising square wave electrical pulses to the skin over a peripheral nerve producing: (1) a propagated nerve action potential (NAP) recorded at a distant point over the same nerve: and (2) a compound muscle action potential (CMAP) arising from the activation of muscle fibres in a target muscle supplied by the nerve. In both cases these may be recorded with surface or needle electrodes.

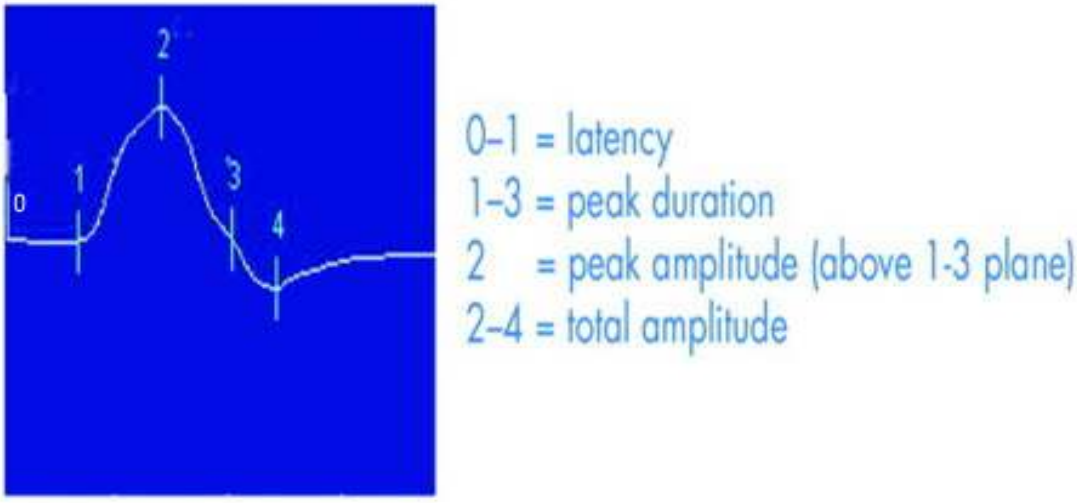
Motor nerve conduction studies : Motor studies are performed by electrical stimulation of a nerve and recording the compound muscle action potential (CMAP) from surface electrodes overlying a muscle supplied by that nerve. The CMAP is a summated voltage response from

the individual muscle fibre action potentials. The recording electrodes are performed using adhesive conductive pads placed onto the skin overlying the target muscle. The active electrode is placed over the muscle belly and the reference over an electrically inactive site (usually the muscle tendon). A ground electrode is also placed somewhere between the stimulating and recording electrodes providing a zero voltage reference point. A supramaximal stimulus is applied to the nerve at a distal and a proximal site. Fastest motor nerve conduction velocity can be calculated as follows: FMNCV (m/s) = distance between stimulation site 1 and site 2 (mm)/[latency site 2 – latency site 1 (ms)].

Sensory conduction studies : The sensory nerve action potential (SNAP) is obtained by electrically stimulating sensory fibres and recording the nerve action potential at a point further along that nerve. Once again the stimulus must be supramaximal. Recording the SNAP orthodromically refers to distal nerve stimulation and recording more proximally (the direction in which physiological sensory conduction occurs). Antidromic testing is the reverse. Different laboratories prefer antidromic or orthodromic methods for testing different nerves.. The sensory latency and the peak to peak amplitude of the SNAP are measured. The velocity correlates directly with the sensory latency and therefore either the result may be expressed as a latency over a standard distance or a velocity.



Nerve Conduction Study



Graph of Motor Nerve Conduction Study

F waves : F waves (F for foot where they were first described) are a type of late motor response. When a motor nerve axon is electrically stimulated at any point an action potential is propagated in both directions away from the initial stimulation site. The distally propagated impulse gives rise to the CMAP. However, an impulse also conducts proximally to the anterior horn cell, depolarising the axon hillock and causing the axon to backfire. This leads to a small additional muscle depolarisation (F wave) at a longer latency. F wave abnormalities can be a sensitive indicator of peripheral nerve pathology, particularly if sited proximally.

Recommended protocol for nerve conduction studies as advised by American association of electrodiagnostic medicine

A simplified NCS protocol may be used for the purpose of defining the presence of distal symmetric polyneuropathy. However, the abbreviated protocol is not sufficient to determine the subtype or severity of the polyneuropathy. For these purposes as well as for clinical trials in which electrodiagnostic measures will be tracked serially, the more comprehensive set of NCSs is recommended.

The simplified NCS protocol is as follows:

1. Sural sensory and peroneal motor NCSs are performed in one lower extremity. Taken together, these NCSs are the most sensitive for detecting a distal symmetric polyneuropathy. If both studies are

normal, there is no evidence of typical distal symmetric polyneuropathy. In such a situation, no further NCSs are necessary.

2. If sural sensory or peroneal motor NCSs are abnormal, the performance of additional NCSs is recommended. This should include NCS of at least the ulnar sensory, median sensory, and ulnar motor nerves in one upper extremity. A contralateral sural sensory and one tibial motor NCS may also be performed according to the discretion of the examiner. Caution is warranted when interpreting median and ulnar studies since there is a possibility of abnormality due to compression of these nerves at the wrist or ulnar neuropathy at the elbow.

3. If a response is absent for any of the nerves studied (sensory or motor), a NCS of the contralateral nerve should be performed.

4. If a peroneal motor response is absent, an ipsilateral tibial motor NCS should be performed.

The minimum case definition criterion for electrodiagnostic confirmation of distal symmetric polyneuropathy is an abnormality (≥99th or ≤1st percentile) of any attribute of nerve conduction in two separate nerves, one of which must be the sural nerve.

Nerve conduction studies (NCS) are the most objective noninvasive measures of nerve function. They represent a valuable tool of evaluation of neuropathy in large clinical and epidemiological studies. In clinical practice, however, NCS should not be considered a substitute for careful clinical examination, because NCS have many pitfalls and their results must be interpreted in the context of clinical data. In the case small-fiber polyneuropathies, the main drawback of NCS is that small myelinated and unmyelinated nerve fibers, which are affected early in the disease course of diabetic neuropathy, do not contribute to the sensory action potential detected by routine NCS. The sensory action potential is altered only after involvement of larger myelinated fibers, which is often a late event in patients with diabetes. Electrophysiological data must, therefore, always be evaluated in a clinical context.

Diabetic retinopathy

Diabetic retinopathy is a well-characterized, sight-threatening, chronic microvascular complication that eventually afflicts virtually all patients with diabetes mellitus. Diabetic retinopathy is characterized by gradually progressive alterations in the retinal microvasculature, leading to areas of retinal non-perfusion, increased vasopermeability, and pathologic intraocular proliferation of retinal vessels.

Epidemiology of diabetic retinopathy

All patients with type 1 diabetes and more than 60% of patients with type 2 diabetes develop some degree of retinopathy after 20 years. In patients with type 2 diabetes, approximately 20% have retinopathy at the time of diabetes diagnosis and most have some degree of retinopathy over subsequent decades about 4% of patients younger than 30 years of age at diagnosis and nearly 2% of patients older than 30 years of age at diagnosis were legally blind.[26] Approximately 25% of patients with type 1 diabetes have retinopathy after 5 years, with this figure increasing to 60% and 80% after 10 and 15 years, respectively.[27]

Pathophysiology

The earliest histologic effects of diabetes mellitus in the eye include loss of retinal vascular pericytes (supporting cells for retinal endothelial cells), thickening of vascular endothelium basement membrane, and alterations in retinal blood flow. With increasing loss of retinal pericytes, the retinal vessel wall develops outpouchings (microaneurysms) and becomes fragile. With time, increasing sclerosis and endothelial cell loss lead to narrowing of the retinal vessels, which decreases vascular perfusion and may ultimately lead to obliteration of the capillaries and small vessels the resulting retinal ischemia is a potent inducer of angiogenic growth factors. These factors promote the

development of new vessel growth and retinal vascular permeability. Proliferating new vessels in diabetic retinopathy have a tendency to bleed, which results in preretinal and vitreous hemorrhages and later macular edema.

Risk factors

1. Duration of diabetes is closely associated with onset and severity of diabetic Retinopathy.[26]
2. Lack of glycemic control.
3. Renal disease, as manifested by microalbuminuria and Proteinuria.[28]
4. Hypertension.[29]
5. Elevated serum lipid levels are associated with extravasated lipid in the retina (hard exudates) and visual loss.[30]

Clinical findings[31]

Clinical findings associated with early and progressing diabetic retinopathy include hemorrhages or microaneurysms (H/Ma), cotton-wool spots (CWSs), hard exudates, intraretinal microvascular abnormalities (IRMAs), and venous caliber abnormalities (VCABs), such as venous loops, venous tortuosity, and venous beading.

The intraretinal hemorrhages can be “flame-shaped” or “dot/blot” like in appearance. IRMAs are either new vessel growth within the retinal

tissue itself or shunt vessels through areas of poor vascular perfusion. It is common for IRMAs to be adjacent to CWSs, which are caused by micro infarcts in the nerve fiber layer. VCABs are a sign of severe retinal hypoxia. In some cases of extensive vascular loss, however, the retina may actually appear free of non-proliferative lesions. Such areas are termed "featureless retina" and are a sign of severe retinal hypoxia.

Symptoms of diabetic retinopathy

1) Patient complaints of blurred vision, usually central vision and metamorphosia as a result of maculopathy with foveal involvement.

2) Black spots, floaters or sudden visual loss may be experienced by patients with vitreous hemorrhage, depending on quantum of bleed.

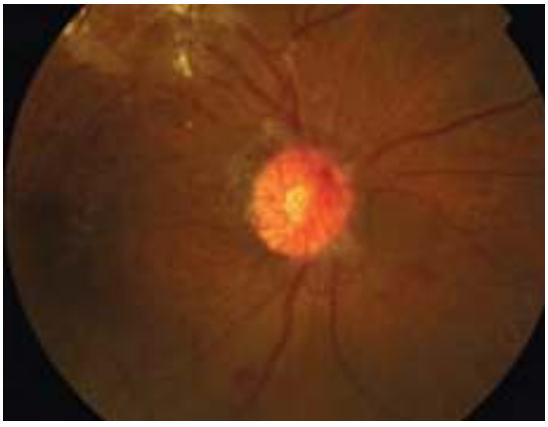
Kanski classification of diabetic retinopathy[31]

1. Background diabetic retinopathy

a. Haemorrhages (Dot and Blot, Flame shaped)
b. Microaneurisms (Located in inner nuclear layer)
c. Hard exudates (Lipoprotien and lipid filled macrophages. Located within the outer plexiform layer).
d. Retinal edema (Located between outer plexiform and inner nuclear layer)


Background Retinopathy : Retinal microaneurysms at the posterior pole; FA shows scattered hyperfluorescent spots in the posterior fundus

Pre-proliferative diabetic retinopathy : Cotton-wool spots, IRMA and venous changes



Severe disc new vessels

Mild new vessels elsewhere

2. Pre proliferative

a. Vascular changes(beading , looping)

b. Dark blot haemorrhages

c. Cottonwool spots

d. Intraretinal microvascular abnormalities

e. Shunt vessels

3. Proliferative

a. Neo vascularisation

b. Fibrous proliferation

c. Vitreous detachment and haemorrhages

4. Maculopathy

a. Focal

b. Diffuse

c. Ischaemic

d. Clinically Significant Macular Oedema (CSMO)

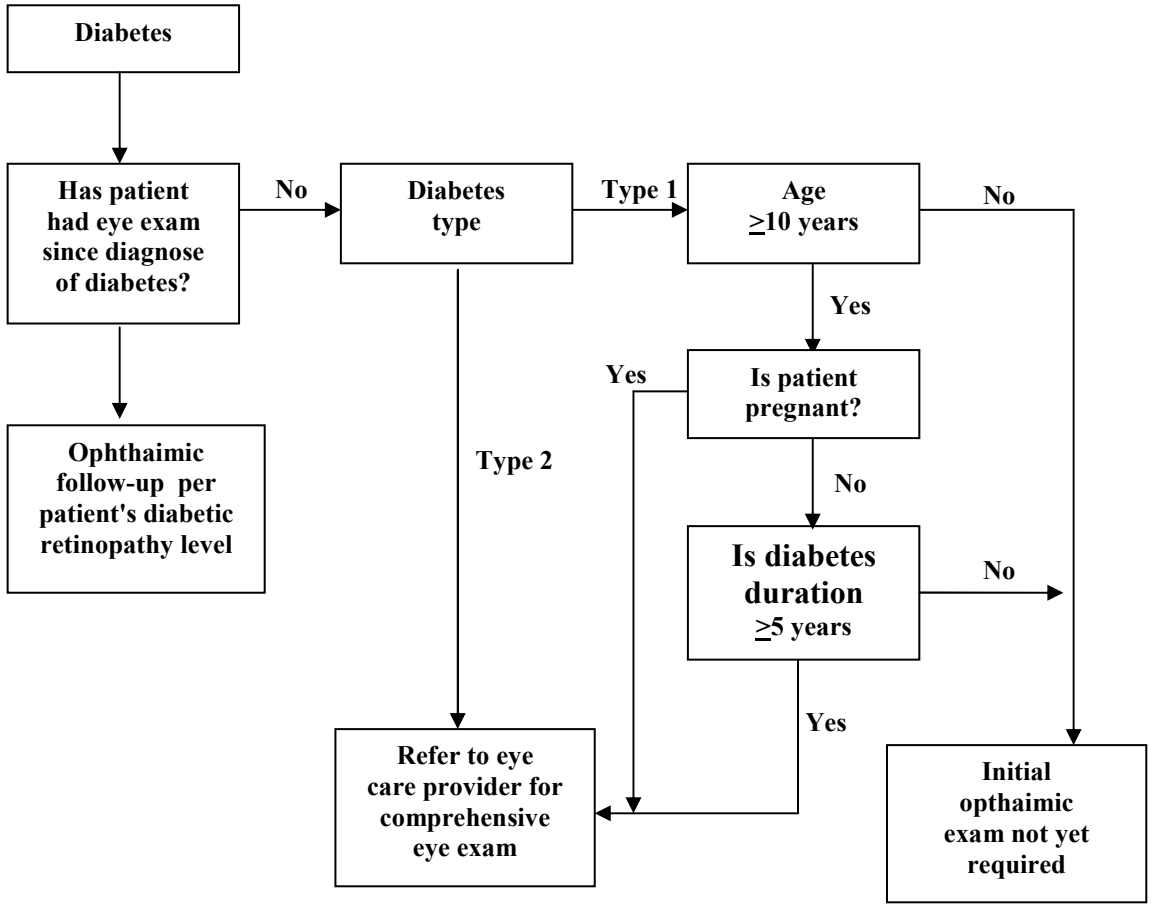
Classification of diabetic maculopathy

Intraretinal

- Macular edema
- Macular hard exudates
- Macular ischaemia

Comprehensive eye examination

Most of the blindness associated with advanced stages of retinopathy can be averted with appropriate and timely diagnosis and therapy.



Diabetic nephropathy

Pathogenisis[30]

Like other microvascular complications pathogenesis of Diabetic nephropathy is related to chronic hyperglycemia. The mechanisms by which chronic hyperglycemia leads to ESRD are :

a) Soluble factors (Growth factors, Angiotensin II, Endothelin, AGEs)
b) Hemodynamic alteration in renal microcirculation.
c) Structural changes in Glomerulus.

Because only 20-40% of patients with diabetes develop Diabetic nephropathy, additional susceptible factors remain unidentified.

Epidemiology

Both type 1 and type 2 diabetes cause renal disease. Compared to type 1, a slightly smaller and imperfectly defined proportion of type 2 patients progress to ESRD, but they represent more than 90% of those receiving renal replacement therapy with the diagnosis of diabetes. The distribution of renal disease due to type 2 diabetes is uneven among racial groups. American Indians, African Americans, and Mexican Americans have a greater incidence than non-Hispanic whites. Genetic predisposition, environmental factors, delayed diagnosis of type 2 diabetes, and sub adequate medical care in minority groups contribute in undefined amounts to such disparity.

Clinical features

Symptoms suggestive of renal impairment :

Oliguria, Anuria, Puffiness of face, Distension of abdomen, Pedal edema.

Nephropathy in type 1 diabetes[33]

The course of diabetic nephropathy can be followed by two main variables:

Proteinuria and GFR.

There are five distinct stages:

1. *Stage 1*: Glomerular hyper filtration and renal enlargement.
2. *Stage 2*: Early glomerular lesions or silent stage with normal albumin excretion. Early glomerular lesions, consisting of glomerular basement membrane thickening and mesangial matrix expansion, characterize the second stage. Those structural changes appear 18 to 36 months after onset of type 1 diabetes and may become prominent after 3.5 to 5 years. During this stage of morphologic changes, microalbuminuria, seen only after exercise or during episodes of very poor metabolic control.

3. Stage 3: Incipient diabetic nephropathy or micro albuminuric stage

Microalbuminuria, defined as 30-300mg per day in a 24 hour collection or 30-300μg/mg of creatinine in spot collection, represents the first laboratory evidence of diabetic renal disease. It is increased by hypertension, strenuous exercise, fever, poor glycemic control, and congestive heart failure. Therefore, a diagnosis of incipient diabetic nephropathy is made only when Microalbuminuria is detected in at least two of three urine specimens over several months.

4. *Stage 4*: Clinical or Overt diabetic nephropathy: proteinuria and falling glomerular filtration rate:

   Albuminuria greater than 300 μg/mg of creatinine relentless decline of renal function, and hypertension define the fourth stage of diabetic nephropathy. This stage, though variable, usually occurs 15 to 20 years after the onset of type 1 diabetes and after 5 or more years of diagnosed type 2 diabetes. The amount of urinary protein can be as little as 500 mg, but it can reach massive proportions, such as 20 to 40 g/24 hours.

5. *Stage 5*: End-stage renal disease.

Nephropathy in type 2 diabetes[32, 33]

Although renal structural changes and severity of target organ damage are similar in both types of diabetes, delayed diagnosis has complicated the construction of the natural history of diabetic renal disease in type 2 diabetes. Hypetension more commonly accompanies in Type II Diabetes.[33]

Materials & Methods

MATERIALS AND METHODS

DESIGN

Cross sectional study

STUDY POPULATION

50 patients with type 2 diabetes attending diabetology OP in Coimbatore medical college hospital from September 2009 to September 2010 were selected for this study after getting informed written consent.

INCLUSION CRITERIA

Patients were included for study if they had

- Onset of type 2 diabetes > 35 years of age.
- Duration of diabetes > 5 yrs.

EXCLUSION CRITERIA

Patients were excluded from study if they had

- Gross albuminuria.
- Non diabetic neuropathies.
- Non diabetic retinopathy and other chronic ophthalmological illness.

Detailed history, complete clinical examination including body mass index, blood pressure and neurological examination with special reference to neuropathic abnormalities using the criteria as stated below,

nerve conduction studies for sensory and motor neuropathy, HbA1C, serum total cholesterol, ophthalmolgical examination for diabetic retinopathy and urine analysis for microalbuminuria was done for all patients.

TECHNIQUES

Assessment and Definition of Diabetic Peripheral neuropathy

In this study the diabetic neuropathy examination (DNE) score is used for assessment of distal symmetrical polyneuropathy.

DIABETIC NEUROPATHY EXAMINATION(DNE) SCORE

Muscle strength

1. Quadriceps femoris: extension of the knee
2. Tibialis anterior: dorsiflexion of the foot

Reflex

3. Triceps surae

Sensation: index finger

4. Sensitivity to pinpricks

Sensation: big toe

5. Sensitivity to pinpricks
6. Sensitivity to touch
7. Vibration perception
8. Sensitivity to joint position

Only the right leg and foot are tested.

Scoring from 0 to 2:

0 = Normal

1 = Mild/moderate deficit

- Muscle strength: Medical Research Council scale 3–4
- Reflex: decreased but present
- Sensation: decreased but present

2 = Severely disturbed/absent

- Muscle strength: Medical Research Council scale 0–2
- Reflex: absent
- Sensation: absent

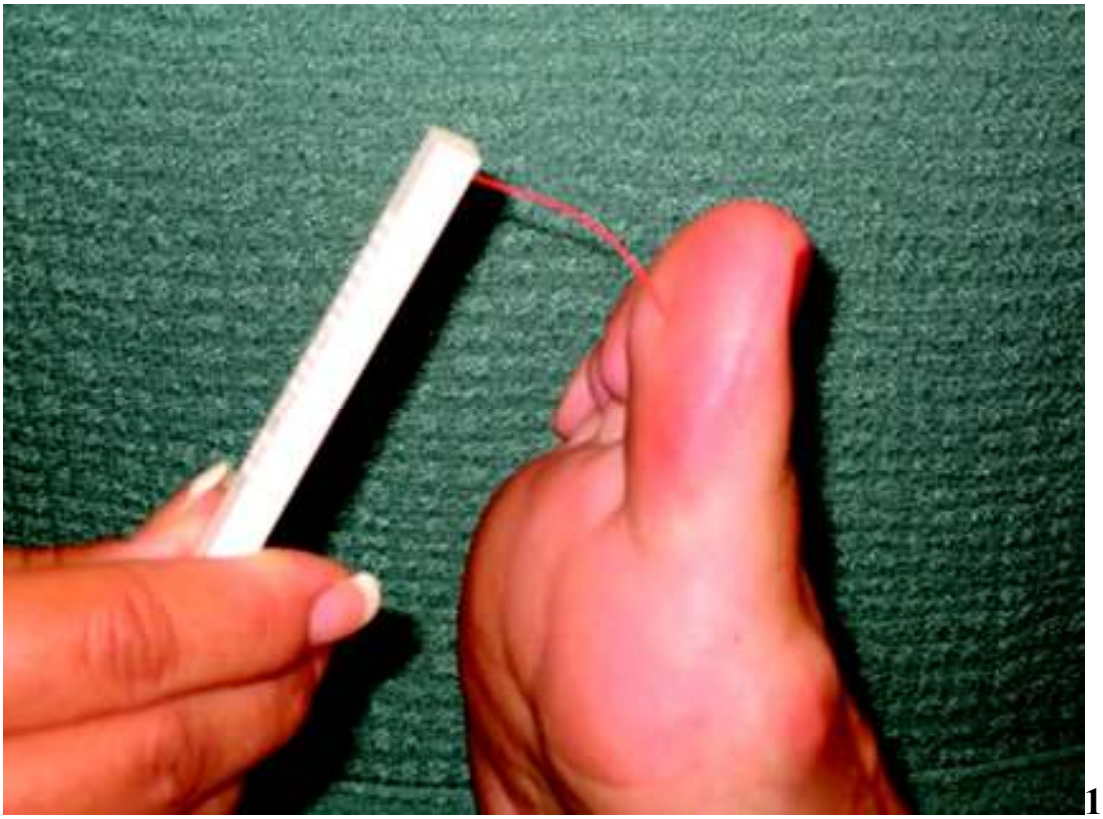
Maximum score: 16 points

A score of > 3 indicates presence of polyneuropathy.

Vibration Sensation: Vibration sensation is performed with the great toe unsupported. Vibration sensation will be tested bilaterally using a 128 Hz tuning fork placed over the dorsum of the great toe on the boney prominence of the DIP joint. Patients, whose eyes are closed, will be asked to indicate when they can no longer sense the vibration from the vibrating tuning fork.In general, the examiner should be able to feel

vibration from the hand-held tuning fork for 5 seconds longer on his distal forefinger than a normal subject can at the great toe (e.g. examiner's DIP joint of the first finger versus patient's toe). If the examiner feels vibration for 10 or more seconds on his or her finger, then vibration is considered decreased. A trial should be given when the tuning fork is not vibrating to be certain that the patient is responding to vibration and not pressure or some other clue. Vibration is scored as 1) present if the examiner senses the vibration on his or her finger for < 10 seconds, 2) reduced if sensed for ≥10 or 3) absent (no vibration detection.)

Muscle Stretch Reflexes : The ankle reflexes will be examined using an appropriate reflex hammer. The ankle reflexes should be elicited in the sitting position with the foot dependent and the patient relaxed. For the reflex, the foot should be passively positioned and the foot dorsiflexed slightly to obtain optimal stretch of the muscle. The Achilles tendon should be percussed directly. If the reflex is obtained, it is graded as present. If the reflex is absent, the patient is asked to perform the Jendrassic maneuver (i.e., hooking the fingers together and pulling). Reflexes elicited with the Jendrassic maneuver alone are designated "present with reinforcement." If the reflex is absent, even in the face of the Jendrassic maneuver, the reflex is considered absent.



10-g Semmes-Weinstein monofilament

Monofilament Testing : For this examination, it is important that the patient's foot be supported (i.e., allow the sole of the foot to rest on a flat, warm surface). The filament should initially be prestressed (4-6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied to the dorsum of the great toe midway between the nail fold and the DIP joint. Do not hold the toe directly. The filament is applied perpendicularly and briefly, (<1 second) with an even pressure. When the filament bends, the force of 10 grams has been applied. The patient, whose eyes are closed, is asked to respond yes if he/she feels the filament. Eight correct responses out of 10 applications is considered normal: one to seven correct responses indicates reduced sensation and no correct answers translates into absent sensation.

Electrophysiological studies will be performed in all cases. The parameters recorded included distal latencies, amplitudes of compound motor action potentials (CMAP), duration of CMAP, F wave latencies and conduction velocities in motor nerves. In sensory nerves, latencies and amplitudes of the sensory nerve action potentials and their conduction velocities were documented.

The presence or absence of neuropathy in these subjects was defined as (Simplified NCS protocol) follows:

5. Sural sensory and peroneal motor NCSs are performed in one lower extremity. Taken together, these NCSs are the most sensitive for detecting a distal symmetric polyneuropathy. If both studies are normal, there is no evidence of typical distal symmetric polyneuropathy. In such a situation, no further NCSs are necessary.
6. If sural sensory or peroneal motor NCSs are abnormal, the performance of additional NCSs is recommended. This should include NCS of at least the ulnar sensory, median sensory, and ulnar motor nerves in one upper extremity. A contralateral sural sensory and one tibial motor NCS may also be performed according to the discretion of the examiner. Caution is warranted when interpreting median and ulnar studies since there is a possibility of abnormality due to compression of these nerves at the wrist or ulnar neuropathy at the elbow.
7. If a response is absent for any of the nerves studied (sensory or motor), a NCS of the contralateral nerve should be performed.
8. If a peroneal motor response is absent, an ipsilateral tibial motor NCS should be performed.

The minimum case definition criterion for electrodiagnostic confirmation of distal symmetric polyneuropathy is an abnormality (≥99th or ≤1st percentile) of any attribute of nerve conduction in two separate nerves, one of which must be the sural nerve.

Assessment and Definition of Diabetic microvascular Complications

Direct ophthalmoscopic examination of fundus

Fundus examination was done and results will be classified as normal, background, pre-proliferative and proliferative retinopathy. It was confirmed by a senior ophthalmologist.

Microalbuminuria detection was done by Albumin Creatinine Ratio estimation. Urinary albumin measured by rate Nephelometry and Urinary Creatinine measured by modified Jaffe's method. Albumin Creatinine Ratio of 30-300 μg/mg of creatinine was defined as microalbuminuria; a ratio greater than 300 μg/mg of creatinine was defined as macroalbuminuria.

Assessment and Definition of various risk factors

The specific risk factors studied were age, sex, duration of diabetes, HbA1C, BMI, systemic hypertension and total serum cholesterol. In the present study the definition of systemic hypertension was taken as subjects with either a history of systemic hypertension on treatment or whose blood pressure measurement shows $\geq$140/90 mm Hg in two different occasions .

Total serum cholesterol >200mg/dl was taken as positive. BMI was calculated as $\frac{\text{Weight in Kg}}{(\text{Height in mt})^2}$ and the normal BMI was 18.5-24.9. HbA1C measured by bidirectionally interfaced fully automated turbidometry by Roche.

Results and Analysis

RESULTS AND ANALYSIS

AGE

The mean age of the study subjects was 51.66 years; standard deviation (SD) of 11.03. Most of the patients belonged to the age group 35-44 yrs

Sex

Out of 50 cases, 36 were males and 14 were females. The ratio of males to females was 2.6:1

TABLE 1

AGE AND SEX DISTRIBUTION

Age (in Yrs)	Male	Female	Total	Percentage(%)
35-44	12	6	18	36
45-54	10	2	12	24
55-64	10	5	15	30
>65	4	1	5	10
TOTAL	36	14	50	

18 patients (36%) in the study were in the age group of 35 – 44 years. Of these 12 were males and 6 were females. 12 patients (24%) were in the age group of 45 – 54 years. Of these 10 were males and 2 were females. 15 patients (30%) in the study were in the 55 – 64 age group, of these 10 were males and 5 were females. 5 patients (10%) were

in the age group of>65 years, of these 4 were males and 1 was female. Most patients were between the age group of 35-44 years.

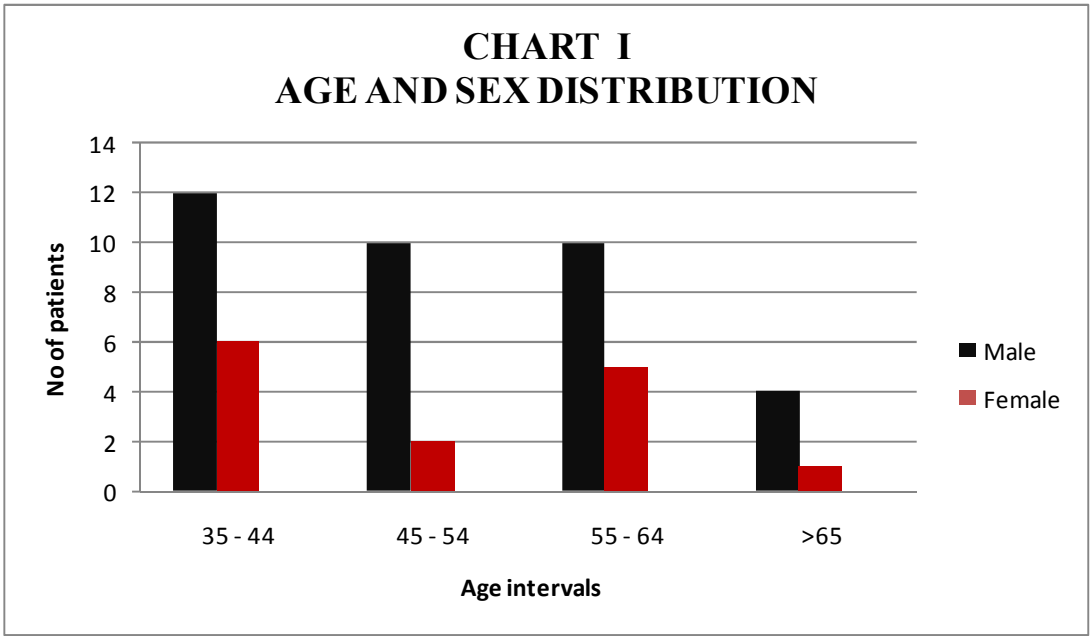
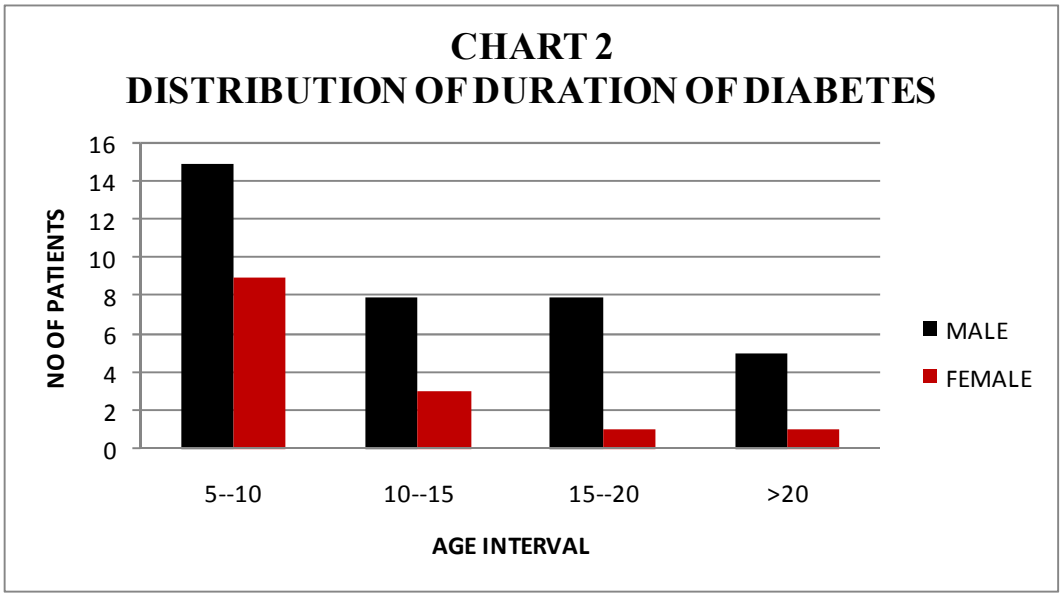


TABLE 2

DISTRIBUTION OF DURATION OF DIABETES MELLITUS

Duration of Diabetes (Yrs)	Male	Female	Total (%)
5-10	15	9	24(48%)
10-15	8	3	11(22%)
15-20	8	1	9(18%)
>20	5	1	6(12%)
TOTAL	36	14	50

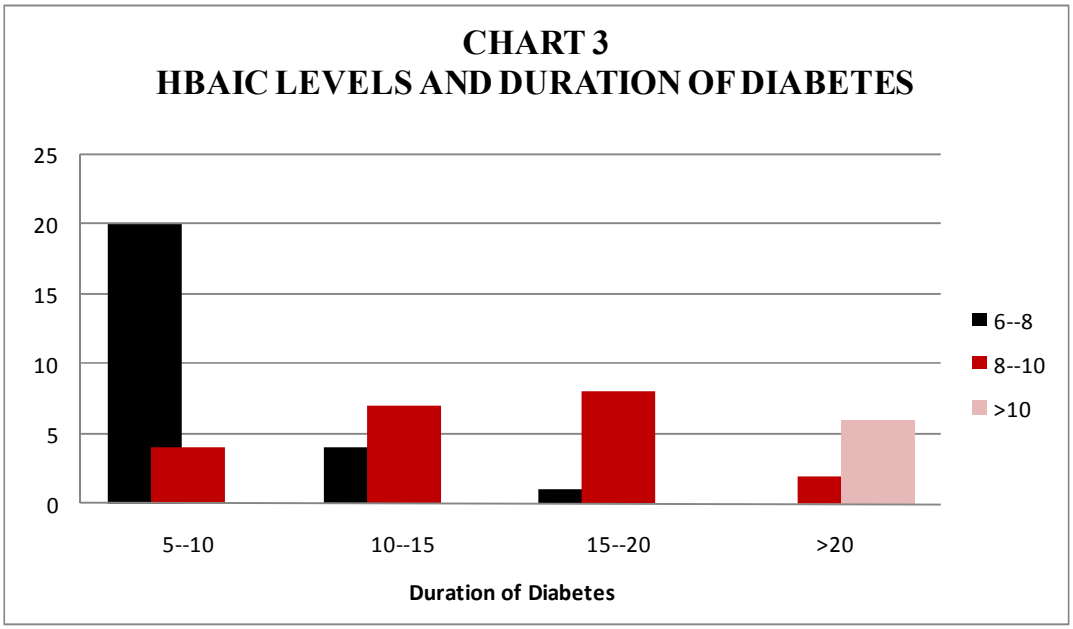


In the study population, more number of patients (24 i.e 48%) were having diabetes with duration 5-10 years, followed by 11 patients (22%) with the duration of 10 to 15 years, next 9 patients(18%) between 15 to 20 years and only 6 patients(12%) were having duration of diabetes >20 yrs.

TABLE 3

HbA1C AND DURATION ON DIABETES

Duration of Diabetes (Years)	HbA1C				
	6-8% (No. of patients)	8-10% (No. of patients)	>10% (No. of patients)	Total	Average HbA1C
5-10	20	4	0	24	7.44
10-15	4	7	0	11	8.27
15-20	1	8	0	9	9.22
>20	0	2	4	6	11.13
TOTAL	25	21	4	50	



Among the 4 patients who had glycosylated hemoglobin >10% all had duration of diabetes >20 years. The average glycosylated hemoglobin (HbA1C) was 7.44,8.27,9.22 and 11.33 for duration of diabetes 5-10 yrs, 10-15 , 15-20 , >20years respectively. This shows that those patients with duration of diabetes more than 10 years have poorer control.

TABLE 4

BODY MASS INDEX

BMI(Kg/M2)	Males	Females	Total	Percentage (%)
18.5-24.9	30	10	40	80%
25-29.9	4	4	8	16%
30-34.9	2	0	2	4%
>35	0	0	0	0

TABLE 5

HYPERTENSION AND DURATION OF DIABETES

Duration of Diabetes (Years)	Number of Hypertensive Patients			
	Male	Female	Total	(%)
6-10	6	1	7	33%
11-15	4	1	5	24%
16-20	4	1	5	24%
>20	3	1	4	19%
TOTAL	17	4	21	

All patients with history of hypertension on antihypertensives and/or whose blood pressure while clinical examination is $\geq$ 140/90 mm Hg on two separate occasions is included in Hypertensive group. Out of total of 50 patients included in study 21 patients were found to be hypertensive. Out of it 17 were males and 4 were females. Out of these 21 patients 33%,24%,24% and 19% were having duration of diabetes 6-10,11-15,16-20,>20 years respectively.

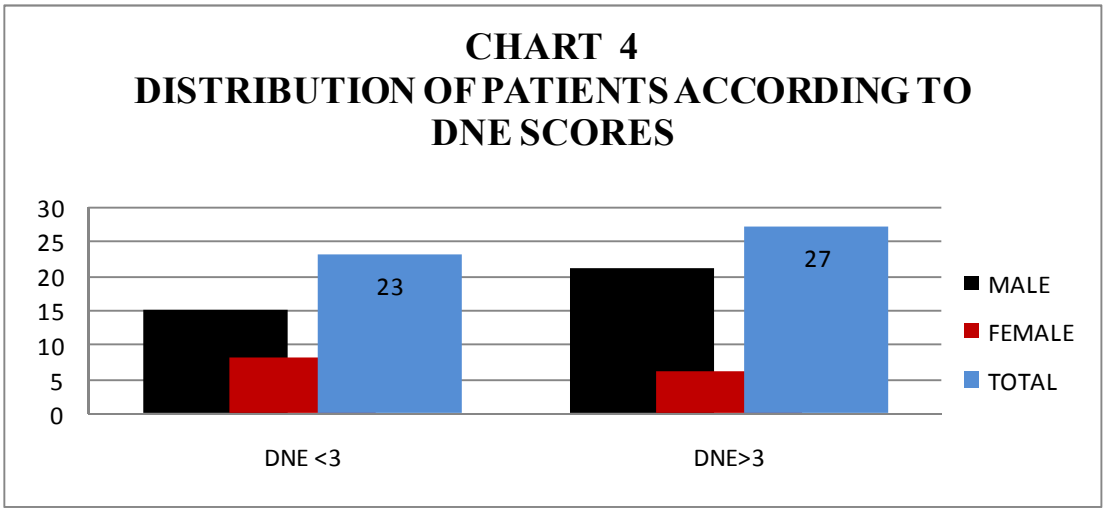
TABLE 6

DISTRIBUTION OF PATIENTS ACCORDING TO DNE SCORES

DNE score	Males	Females	Total	(%)
$\leq$3	15	8	23	46%
4-8	12	1	13	26%
9-12	6	4	10	20%
13-16	3	1	4	8%

According to definition those patients with DNE score > 3 is having diabetic peripheral neuropathy (DSPN).

DNE score	Male	Female	Total	(%)
≤3	15	8	23	46%
>3	21	6	27	54%



So, in this study out of total 50 patients, 27 (54%)patients were found to have peripheral neuropathy. Among them 21 were males and 6 were females. Out of total 36 males in the study 21 patients(58%) had DNE scores >3 and out of total 14 females in the study 6 patients (43%) had DNE scores >3.

TABLE 7

TOTAL SERUM CHOLESTEROL

Total Cholesterol	Male	Female	Total	Percentage
>200 mg/dl	30	8	38	76%
≤200mg/dl	6	6	12	24%

Out of total 50 patients 38(76%) were found to have total cholesterol >200 mg/dl.

TABLE 8

DIABETIC RETINOPATHY

Retinopathy	**Males**	**Females**	**Total**	**Percentage**
Background	6	4	10	20%
Pre-proliferative	5	3	8	16%
Proliferative	2	1	3	6%

Out of total 50 patients in the study, 21 (42%) patients were found to have diabetic retinopathy. Distribution of various types of retinopathy are as given in the following table 20% ,16% and 65 of the patients with diabetic retinopathy had background, pre-proliferative and proliferative retinopathy respectively.

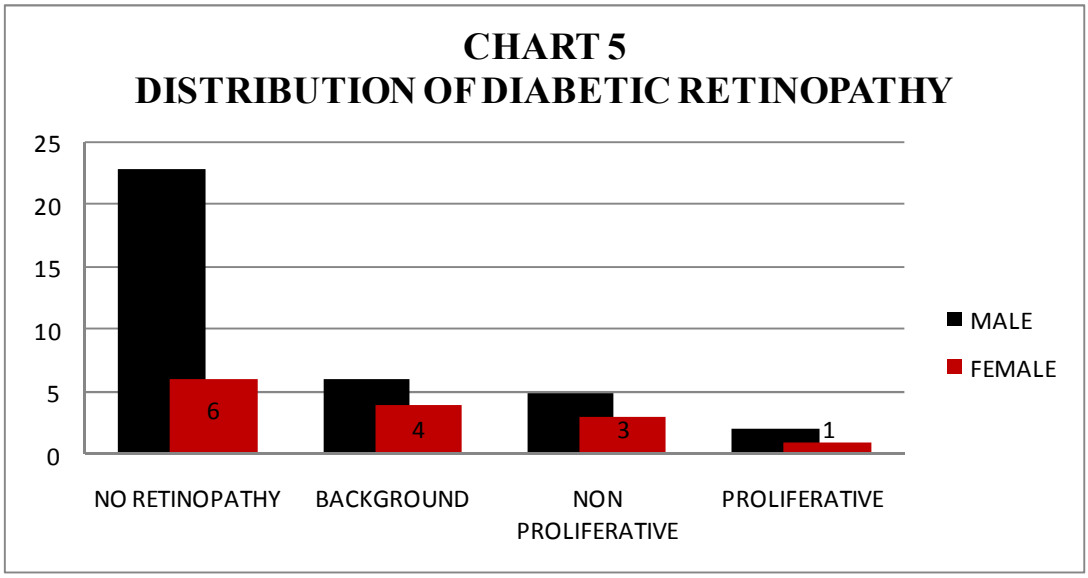
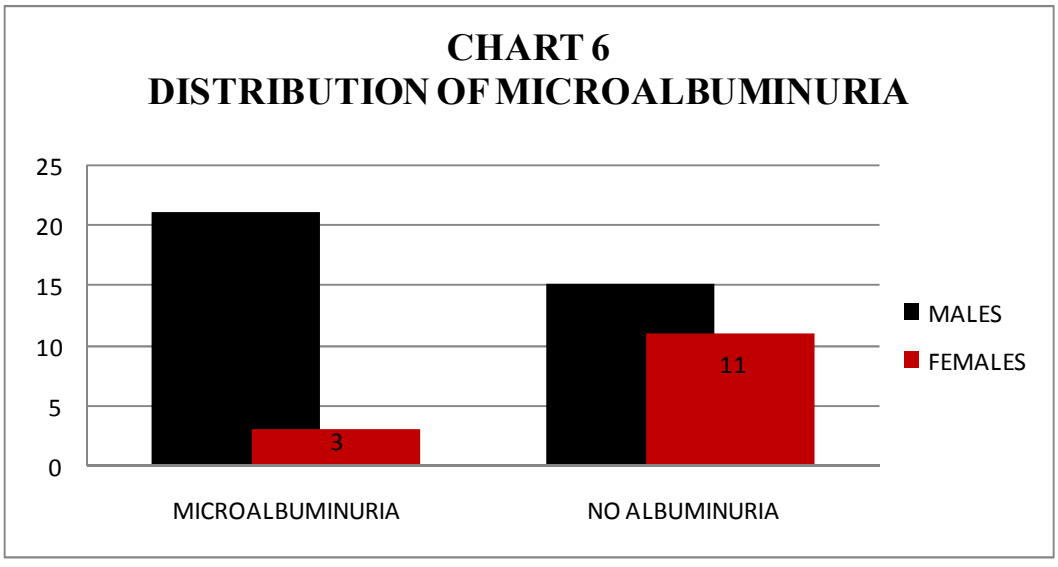


TABLE 9

MICROALBUMINURIA

	Males	Females	Total	Percentage
Microalbuminuria present	21	3	24	48%
Microlbuminuria not present	15	11	26	52%



Out of total 50 patients 24 (48%) had microalbuminuria. As mentioned before those patients with gross albuminuria were excluded from study.It is seen from the graph that out of total 36 male patients in this study 21(58%) had microalbuminuria while out of 14 female patients in this study only 3(6%) had microalbuminuria. So microalbuminuria is more common in males.

TABLE 10

NERVE CONDUCTION STUDY

	Males	**Females**	**Total**	**Percentage(%)**
NCS Positive	22	7	29	58%
NCS Negative	14	7	21	42%

Nerve conduction study was done on all patients using the standard protocol already mentioned. By using this method 29 (58%) patients were found to have peripheral neuropathy (positive). Out of this 22 were males and 7 were females.

TABLE 11

COMPARATIVE ANALYSIS OF CLINICAL EXAMINATION SCORE(DNE) AND NERVE CONDUCTION STUDY

	Diabetic Peripheral Neuropathy					
	DNE Score≤3(Positive)			**DNE Score>3(Negative)**		
	Males	**Females**	**Total(%)**	**Males**	**Females**	**Total(%)**
NCS Positive	2	1	**3(10.3%)**	20	6	**26(89.7%)**
NCS Negative	13	7	**20(95.2%)**	1	0	**1(4.8%)**

From this table X^2=35.338 and P value was found to be 0.001,thus statistically highly significant.

From this table it can be seen that out of total 29 patients found to have peripheral neuropathy by nerve conduction study 26 (89.7%) of them had DNE scores >3 and so only 3(10.3%) patients were found to have peripheral neuropathy by nerve conduction who were missed by our clinical examination score. But it can also be seen from the table that 1 patient(4.8%) who was found by nerve conduction as not having peripheral neuropathy was found to have DNE score >3 and thus was clinically positive for neuropathy.

CHART 7
COMPARITIVE STUDY OF DNE SCORES AND NERVE CONDUCTION

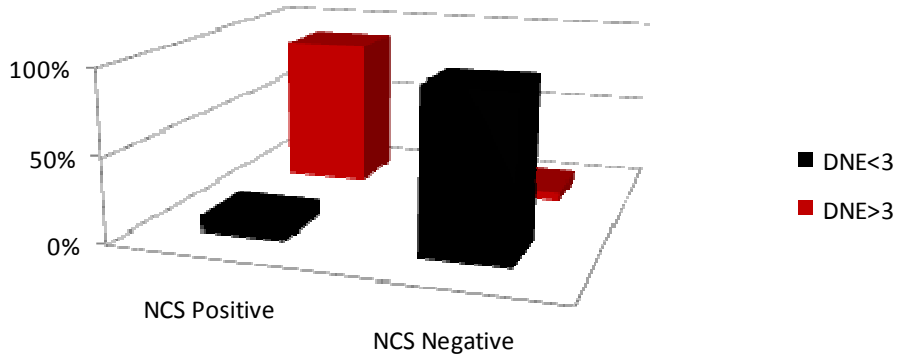


TABLE 12

DIABETIC PERIPHERAL NEUROPATHY AND RETINOPATHY

	Diabetic Peripheral Neuropathy					
	DNE Score≤3			DNE Score>3		
	Males	Female	Total(%)	Male	Female	Total(%)
Diabetic retinopathy	5	2	**7(33.3%)**	13	2	**14(66.7%)**
No retinopathy	10	6	**16(55.2%)**	8	4	**13(44.8%)**

From this table chi-square value X^2=5.339 and P value was <0.05 and thus this association was statistically significant.

Out of 21 patients who were found to have retinopathy by fundus examination 14 patients(66.7%) had peripheral neuropathy by clinical examination (DNE)score while 16 (55.2%) out of 29 patients those who did not have retinopathy also did not have peripheral neuropathy.

On calculating correlation between these two variables, Pearsons correlation coefficient r=0.416 (p 0.05) and thus it was found that correlation between diabetic peripheral neuropathy and diabetic retinopathy was also statistically significant.

CHART 8
DIABETIC PERIPHERAL NEUROPATHY AND RETINOPATHY

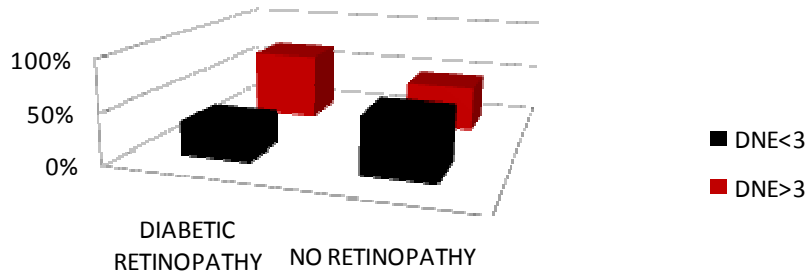


TABLE 13

DIABETIC PERIPHERAL NEUROPATHY AND MICROALBUMINURIA

	Diabetic Peripheral Neuropathy					
	DNE score≤3			DNE score>3		
	Male	Female	Total	Male	Female	Total
Micro Albuminuria	3	1	**4(16.7%)**	18	2	**20(83.3%)**
No albuminuria	12	7	**19(73.1%)**	3	4	**7(26.9%)**

From this table X^2=15.987 and P value was 0.001and thus this association highly significant.

Out of 24 patients who were found to have microalbuminuria ,20(83.3%) had peripheral neuropathy by DNE scores, while 19 (73.1%) out of 26 patients those who did not have microalbuminuria also did not have peripheral neuropathy.

On calculating correlation between these two variables, Pearsons correlation coefficient r=0.565 (p 0.01) and thus it was found that correlation between diabetic peripheral neuropathy and microalbuminuria was also statistically significant.

CHART 9
DIABETIC PERIPHERAL NEUROPATHY AND MICROALBUMINURIA

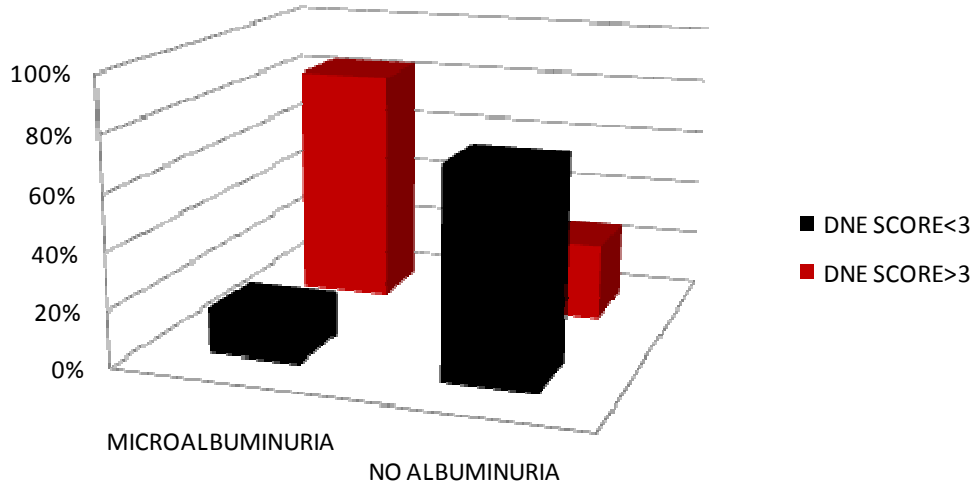


TABLE 14

DIABETIC PERIPHERAL NEUROPATHY AND SEX

	Diabetic Peripheral Neuropathy	
	DNE Score≤3	**DNE Score>3**
Males	15(41.7%)	21(58.3%)
Females	8(57.1%)	6(42.9%)

From this table X^2=0.972and P value was 0.324 and thus this association not statistically significant.

On calculating correlation between these two variables, Pearsons correlation coefficient r=0.197 and thus it was found that correlation between diabetic peripheral neuropathy and sex was not statistically significant.

TABLE 15

DISTRIBUTION OF DIABETIC PERIPHERAL NEUROPATHY IN DIFFERENT AGE GROUPS

	Diabetic Peripheral Neuropathy					
	DNE Score≤3			**DNE Score>3**		
Age interval	**Males**	**Females**	**Total(%)**	**Males**	**Females**	**Total(%)**
35-44	7	5	**12(66.7%)**	5	1	**6(33.3%)**
45-54	2	1	**5(41.7%)**	8	1	**7(58.3%)**
55-64	4	2	**4(26.7%)**	6	3	**11(73.3%)**
>65	2	0	**2(40%)**	2	1	**3(60%)**

From this table X^2=8.515 and P value was <0.05 and thus this association statistically significant.

The mean age of patients with peripheral neuropathy was found to be 54.67 and the mean age of patients without peripheral neuropathy was found to be 46.78 . In the age groups 35-44,45-54,55-64 and >65 ,it was found that out of total number of patients in each groups, 33.3%, 58.3%, 73.3%, 60% had diabetic neuropathy respectively.

On calculating correlation between these two variables, Pearsons correlation coefficient r=0.841 (p 0.05) and thus it was found that correlation between diabetic peripheral neuropathy and age was statistically significant.

CHART 10
DISTRIBUTION OF DIABETIC NEUROPATHY IN DIFFERENT AGE GROUPS

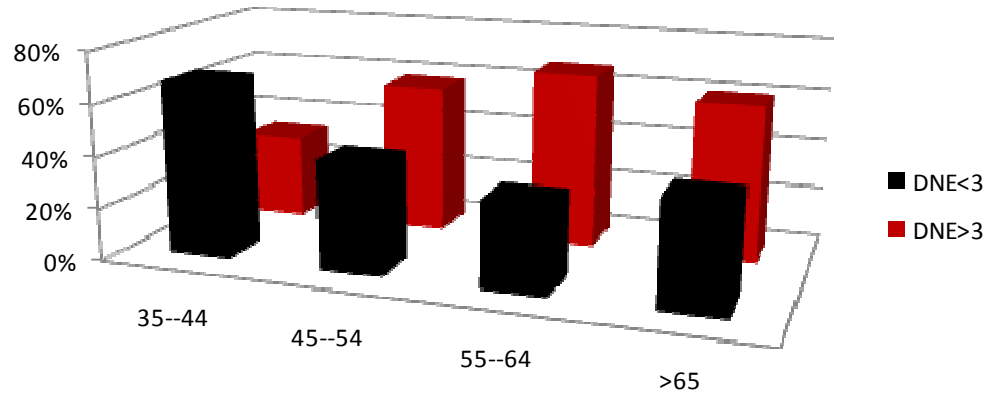


TABLE 16

DIABETIC PERIPHERAL NEUROPATHY AND DURATION OF DIABETES

	Diabetic Peripheral Neuropathy					
	DNE Score≤3			DNE Score>3		
Duration of diabetes	**Males**	**Females**	**Total(%)**	**Males**	**Females**	**Total(%)**
5-10	10	5	**16(66.7%)**	5	4	**8(33.3%)**
10-15	2	3	**4(36.4%)**	6	0	**7(63.6%)**
15-20	2	0	**2(22.2%)**	6	1	**7(77.8%)**
>20	1	0	**1(16.7%)**	4	1	**5(83.3%)**

From this table X^2=8.665 and P value <0.05 was and thus significant.

The mean duration of diabetes in patients with peripheral neuropathy was found to be 13.98 and the mean duration in those without peripheral neuropathy was found to be 10.10 Among those patients with duration of diabetes >20 years 83% had peripheral neuropathy. Similarly 78%,64%,33% of patients with duration of diabetes 5-10,10-15,15-20 years respectively had peripheral neuropathy.

On calculating correlation between these two variables, Pearsons correlation coefficient r=0.400 (p 0.01) and thus it was found that correlation between diabetic peripheral neuropathy and duration of diabetes was also statistically significant.

CHART 11
DIABETIC PERIPHERAL NEUROPATHY AND DURATION OF DIABETES

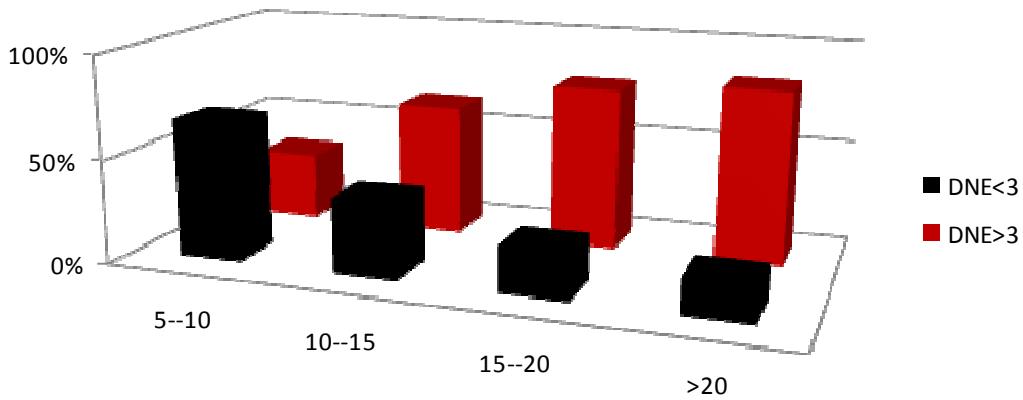


TABLE 17

DIABETIC PERIPHERAL NEUROPATHY AND HbA1C LEVELS

	Diabetic Peripheral Neuropathy					
	DNE Score≤3(negative)			DNE Score>3(positive)		
HbA1C(%)	**Males**	**Females**	**Total(%)**	**Males**	**Females**	**Total**
6-8	11	5	**16(64%)**	7	2	**9(36%)**
8-10	3	3	**6(28.6%)**	12	3	**15(71.4%)**
>10	1	0	**1(25%)**	2	1	**3(75%)**

From this table X^2=6.539 and P value was <0.05 and thus significant.

The mean HbA1C level of patients with peripheral neuropathy was 9.22 with and those without peripheral neuropathy was 7.65.

On calculating correlation between these two variables, Pearsons correlation coefficient r=0.337 (p 0.05) and thus it was found that correlation between diabetic peripheral neuropathy and HbA1C was also statistically significant.

CHART 12
PERIPHERAL NEUROPATHY AND HbA1C LEVELS

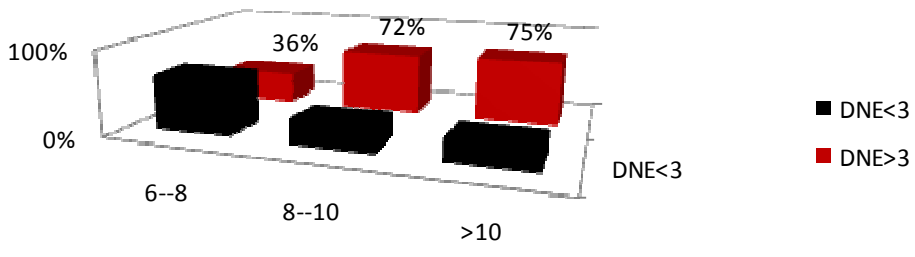


TABLE 18

DIABETIC PERIPHERAL NEUROPATHY AND BODY MASS INDEX

	Diabetic Peripheral Neuropathy					
	DNE Score≤3			DNE Score>3		
BMI(Kg/m2	**Males**	**Females**	**Total(%)**	**Males**	**Females**	**Total**
18.5-24.9	12	7	**20(50%)**	18	3	**20(50%)**
25-29.9	2	1	**3(37.5%)**	2	3	**5(62.5%)**
30-34.9	1	0	**0**	1	0	**2(100%)**
>35	0	0	**0(%)**	0	0	**0(%)**

From this table X^2=2.194 and P value was 0.334 and thus not significant.

The mean BMI in patients with peripheral neuropathy was 23.05 and in those without peripheral neuropathy was 22.76.

On calculating correlation between these two variables, Pearsons correlation coefficient r=0. 197 and thus it was found that correlation between diabetic peripheral neuropathy and BMI was also not statistically significant.

CHART 13
DIABETIC PERIPHERAL NEUROPATHY AND BMI

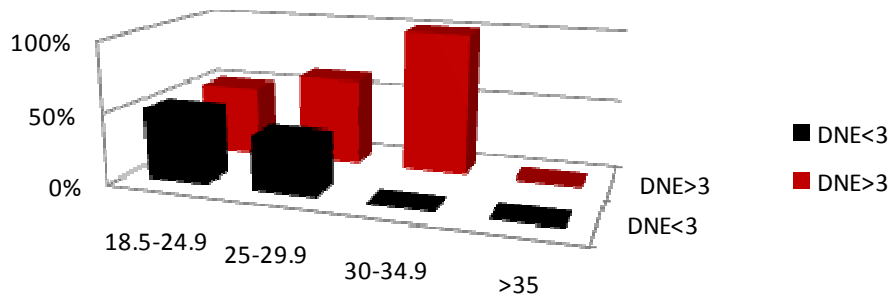


TABLE 19

DIABETIC PERIPHERAL NEUROPATHY AND SYSTEMIC HYPERTENSION

	Diabetic Peripheral Neuropathy					
	DNE Score≤3			DNE Score>3		
	Males	**Females**	**Total**	**Males**	**Females**	**Total**
Hypertensive	1	0	**3(14.3%)**	16	4	**18(85.7%)**
Normal BP	14	8	**20(69%)**	5	2	**9(31%)**

From this table X^2=14.661 and P value was <0.001and thus highly significant.

Out of the total 21 patients who were found to have systemic hypertension, 18 (85.7%)had peripheral neuropathy. Also out of total 29 patients who were found as having normal blood pressure 20(69%)were not having peripheral neuropathy.

On calculating correlation between these two variables, Pearsons correlation coefficient r=0.541 (p 0.05) and thus it was found that correlation between diabetic peripheral neuropathy and systemic hypertension was also statistically significant.

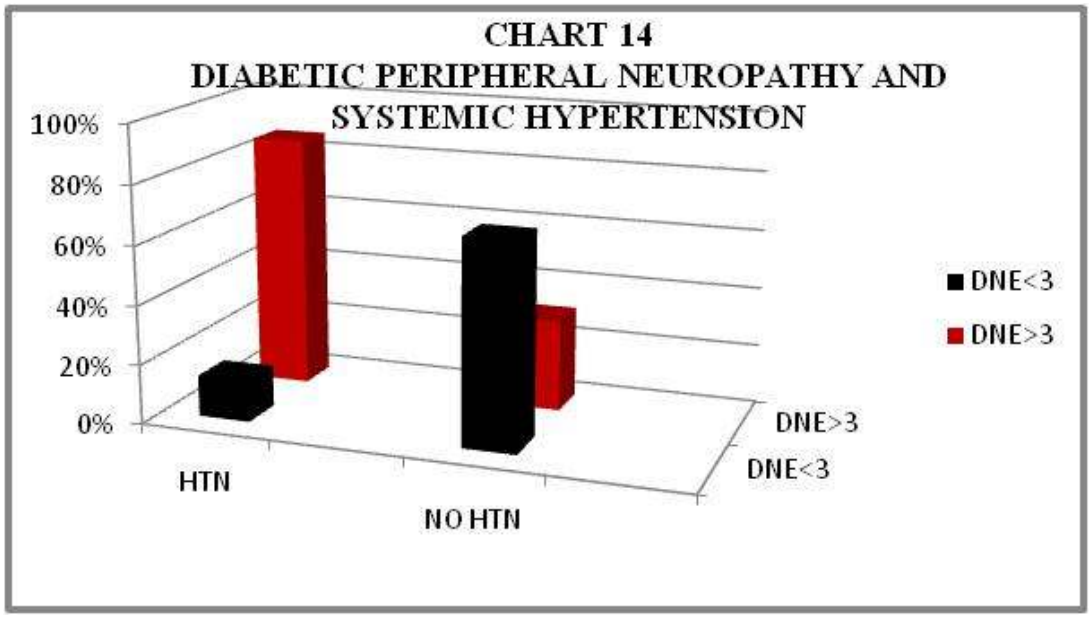


TABLE 20

DIABETIC PERIPHERAL NEUROPATHY AND TOTAL SERUM CHOLESTEROL

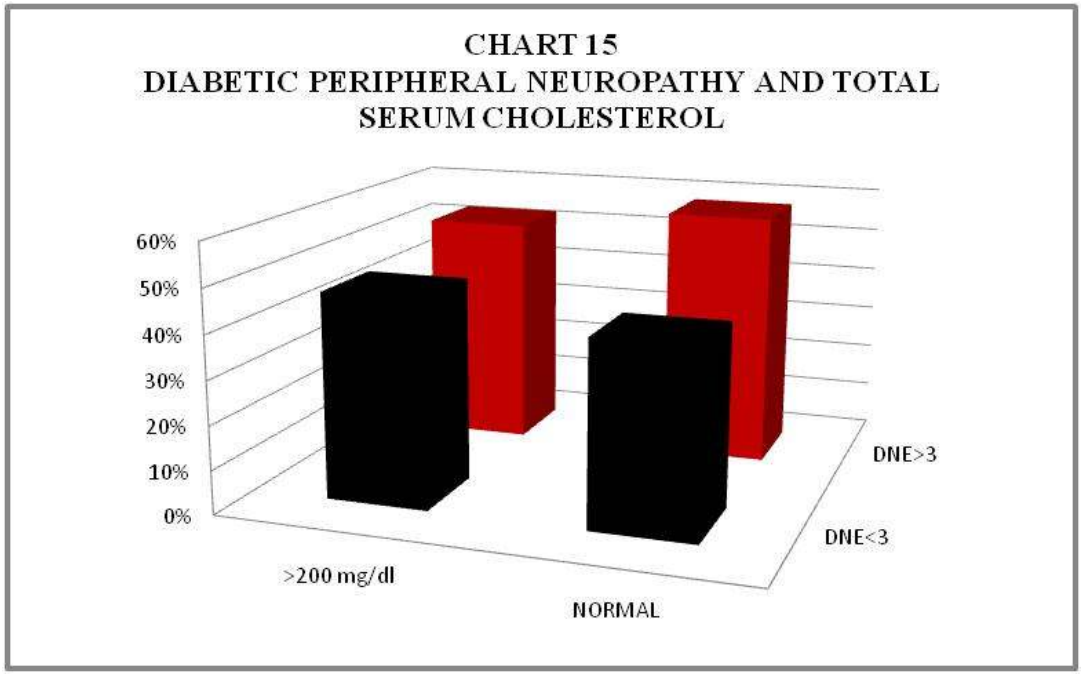
	Diabetic Peripheral Neuropathy					
	DNE Score≤3			DNE Score>3		
Total Serum Cholesterol	**Males**	**Females**	**Total(%)**	**Males**	**Females**	**Total(%)**
>200 mg/dl	12	6	**18(47.4%)**	16	4	**20(52.6%)**
NORMAL	3	2	**5(41.7%)**	5	2	**7(58.3%)**

From this table X^2=0.119 and P value was 0.730 and thus not significant.

Out of total 38 patients who were found to be having high total serum cholesterol,20(53%) of them had peripheral neuropathy. But out

of 12 patients who were having normal serum cholesterol 7(58.3%) were having peripheral neuropathy.

On calculating correlation between these two variables, Pearsons correlation coefficient r=0.049 and thus it was found that correlation between diabetic peripheral neuropathy and total serum cholesterol was also not statistically significant.



Discussion

DISCUSSION

Diabetic Neuropathy is one of the most common troublesome complications of diabetes mellitus.

One of the aims of the present study was clinical and electrophysiological evaluation of diabetic peripheral neuropathy and do a comparative analysis. The present study used the Diabetic Neuropathy Examination Score (DNE), which was designed by Meijer. Nerve conduction studies were done according to a standard protocol as already mentioned. In the study it was observed that out of the 29 subjects who were found to have neuropathy by Nerve Conduction Studies, 26 tested positive by the DNE score which gave a sensitivity of 89.7%. There is statistically significant association between clinical examination scores(DNE) and nerve conduction study. Thus it can be inferred that the clinical examination by the DNE scores is a simple, reliable and reproducible method of diagnosing diabetic peripheral neuropathy.

Similar results were observed in various previous studies. In an earlier study done by **M K ROY** et al[35] in Kolkata in 2002, it was found that the nerve conduction studies were found to be abnormal only in those with clinical abnormalities as per DNE scoring. In another study which was done by **A.MYTHILI** et al[23] which was published in

International Journal Of Diabetes In Developing Countries in 2010,it was found that out of the 71 subjects who were confirmed to have neuropathy by Nerve Conduction Studies, 59 tested positive by the DNE score which gave a sensitivity of 83%. Of the 29 subjects who were considered as not having neuropathy by the same criteria, 6 had a DNE score positive for neuropathy. The specificity of the DNE score was 79%.

One study which showed results which were contrary to our observations done by **KUMAR R** et al[36] in Delhi which showed that out of 50 patients of type 2 diabetes, clinical neuropathy was present in 40% cases, but using nerve conduction abnormalities as a measure of neuropathy prevalence increases to 68% and was statistically highly significant ($p = 0.001$).This disparity may be due to the fact that they used a different clinical scoring other than the DNE scoring used in our study, which might have lesser sensitivity and specificity.

CORRELATION BETWEEN DIABETIC NEUROPATHY AND OTHER MICROVASCULAR COMPLICATIONS

The second aim of this study was to correlate diabetic neuropathy with retinopathy and microalbuminuria. For this correlation clinical examination scoring was used for defining the presence or absence of peripheral neuropathy. As already mentioned those patients with gross albuminuria and those with retinopathy due to other causes were excluded

from study.It was found that there is statistically significant correlation between diabetic neuropathy and retinopathy ($P<0.05$) and microalbuminuria ($P<0.001$)

This finding was similar to that observed in earlier studies. **TESFAYE S** et al[37] in the in the European Diabetes (EURODIAB) Prospective Complications Study showed evidence of a strong association between neuropathy and other microvascular complications. In the study conducted by **KUMAR R** et al in Delhi it was shown that all patients with diabetic retinopathy and 86% of patients with microalbuminuria were found to have peripheral neuropathy which were statistically significant. In a study by **PIRART**[38] showed positive correlation between the occurrence of diabetic neuropathy and retinopathy.

This strong correlation between various microvascular complications of diabetes further supports the fact that there is a common pathogenic mechanism underlying. Therefore by early detection of peripheral neuropathy, urgent measures can be taken to retard the progression of other microvascular complications.

CORRELATION BETWEEN PERIPHERAL NEUROPATHY AND VARIOUS RISK FACTORS

From the present study it was found that there was statistically significant correlation between diabetic peripheral neuropathy with age ($p< 0.05$), duration of diabetes ($P<0.01$), HbA1C levels($P< 0.05$) and systemic hypertension ($P<0.01$).It was also found that the correlation of diabetic peripheral neuropathy with sex, BMI total serum cholesterol was not statistically significant.

One of the earlier study to establish relation between glycemic control and neuropathy performed by **PIRART**[38] which showed that poor control was associated with a higher incidence of neuropathy. Intensive glycemic control in the DCCT study showed decreased incidence of diabetic neuropathy to 3% in intensively treated patients compared to 10% in group that received conventional treatment.[5] **HOLMAN** et al[39], concluded that tight control of diabetes retarded or reversed the progression of the neuropathy. On the other hand Service et al[40], found no such correlations. However majority of the authorities DYCK et al, favour the view that poor control of diabetes is associated with an increased risk of neuropathy. This is further substantiated by our study by the strong correlation of neuropathy with duration of diabetes and HbA1C .

TESFAYE S et al showed that the incidence of neuropathy is associated with potentially modifiable cardiovascular risk factors,

including a raised triglyceride level, body-mass index, smoking, and hypertension. In the study by **KUMAR** et al it was found that in type 2 diabetics, age, duration of diabetes, microalbuminuria and retinopathy were strongly correlated with deterioration of nerve function

With respect to systemic hypertension and age the observations made in the present study was similar to previous studies**.** Aggressive treatment of hypertension is now standard clinical practice in the management of nephropathy and retinopathy, and the results of the present study make a case for clinical trials to confirm the efficacy of antihypertensive agents and possibly other strategies for cardiovascular risk reduction in slowing the progression of neuropathy.

In this study out of total 50 patients, only two of them had BMI >30.That may account for the disparity in the observations in our study compared to Tesfaye.s.et al. In the present study correlation was done between total cholesterol levels and neuropathy while in Tesfaye. S .et al they compared the triglyceride levels .Furthermore there may be other factors influencing serum cholesterol which was not taken into consideration in the present study. In the previous studies correlations were done with peripheral neuropathy assessed by nerve conduction studies, but in the present study peripheral neuropathy assessed by clinical scoring was used for comparison. All these factors may be responsible for the disparity.

Conclusions

CONCLUSIONS

1. There is statistically significant association between clinical examination scores(DNE) and nerve conduction study. Thus it can be inferred that the clinical examination by the DNE scores is a simple, reliable and reproducible method of diagnosing diabetic peripheral neuropathy.
2. There is statistically significant correlation of diabetic neuropathy with other microvascular complications namely diabetic retinopathy($P<0.05$)and microalbuminuria ($P<0.001$)
3. There was statistically significant correlation between diabetic peripheral neuropathy with age ($p< 0.05$), duration of diabetes ($P<0.01$), HbA1C levels ($P<0.05$) and systemic hypertension ($P<0.01$). It was also found that the correlation of diabetic peripheral neuropathy with sex, BMI, total serum cholesterol was not statistically significant.

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Annexures

PROFORMA

PRELIMINARY DATA OF THE PATIENT

NAME : DATE :

AGE/SEX : I.P. NO. :

DEPARTMENT : UNIT :

WARD :

OCCUPATION :

DATE OF ADMISSION :

DATE OF DISCHARGE:

ADDRESS :

PRESENTING COMPLAINTS :

5. Symptoms of unsteadiness in walking? YES/No
6. Do you have a burning, aching pain or tenderness of your legs or feet? YES/NO
7. Do you have pricking sensations at your legs and feet? YES/NO
8. Do you have places of numbness on your legs or feet? YES/NO

PAST HISTORY:
Previous H/o Illness

TREATMENT HISTORY:

PERSONAL HISTORY :

H/o Alcohol Intake : Yes ☐ No ☐
Duration :
Quantity :

H/o of Smoking : Yes ☐ No ☐

Duration :
Quantity :

H/o of Weight Loss :

FAMILY HISTORY :

Diabetes : Yes ☐ No ☐

Hypertension : Yes ☐ No ☐

GENERAL PHYSICAL EXAMINATION:

Height: Cms.

Weight: Kgs

B.M.I. :

Pallor - Yes ☐ No ☐

Icterus - Yes ☐ No ☐

Clubbing - Yes ☐ No ☐

Cyanosis - Yes ☐ No ☐

Lymphadenopathy - Yes ☐ No ☐

VITAL PARAMETERS:
Pulse _____ BP _____
Respiratory Rate _____
Temperature _____

SYSTEMIC EXAMINATION:
CENTRAL NERVOUS SYSTEM:
Higher Mental functions :

Cranial Nerves :
Fundoscopy :

Muscle strength	**0**	**1**	**2**
1. Quadriceps femoris:	☐	☐	☐
2. Tibialis anterior:	☐	☐	☐
Reflex			
3. Triceps surae	☐	☐	☐
Sensation: index finger			
4. Sensitivity to pinpricks	☐	☐	☐
Sensation: big toe			
9. Sensitivity to pinpricks	☐	☐	☐
10. Sensitivity to touch	☐	☐	☐
11. Vibration perception	☐	☐	☐
8. Sensitivity to joint position	☐	☐	☐

CARDIOVASULAR SYSTEM

Positive Findings:

RESPIRATORY SYSTEM

Positive Findings:

GASTROINTESTINAL SYSTEM

Positive findings:

INVESTIGATIONS

1. Blood a. Hb% c. T.C.
   b. ESR d. DC-N/LM/E/B.

2. Urine

a. Quantity in 24 hours

b. Colour of the urine

c. Specific gravity

d. Reaction: Acidic / Alkaline

e. Sugar

f. Albumin / Microalbuminuria detection by
Albumin creatinine ratio estimation

g. 24 hrs urine protein

h. Ketone bodies

i. Microscopic

4. Diabetic Profile :

RBS
FBS
PPBS (2 hrs. after food)
HbAIc

5.Total S. Cholesterol :

6. Renal Function Tests:

B. Urea.
S. Creatinine
S. Sodium
S. Potassium

7. ECG in all 12 leads :

8. Chest X-Ray

9.NERVE CONDUCTION STUDY:

SL NO	AGE	SEX	IP NO	SYMPTOM SCORE	PAST HISTORY	FAMILY HISTORY	DURATION OF DIABETES	SMOKING	ALCOHOLISM	BMI	PULSE RATE	SYSTEMIC HYPERTENSION	CLINICAL (DNE) SCORES	CVS	FUNDUS	MICRO ALBUMINURIA	FBS	PPBS	HBA1C	TOTAL CHOLESTEROL >200mg/dl	ECG	CHEST XRAY	NERVE CONDUCTION STUDY
1	53	F	60224	2	NS	+	6	NO	NO	NL	70	NO	6	N	NL	NO	233	358	6.1	NO	N	N	+
2	46	M	1447	1	NS	+	6	NO		NL	80	NO	2	N	NL	NO	168	215	7	NO	N	N	-
3	38	M	40991	1	NS	-	8	NO	YES	NL	86	NO	2	N	NL	NO	291	336	7.3	NO	N	N	-
4	63	F	3983	1	NS	+	16	NO	NO	26.9	84	NO	1	N	NPR	YES	145	170	9.7	YES	N	N	-
5	63	F	4907	4	SHT	+	22	NO	NO	26.6	78	YES	14	N	NPR	YES	180	260	9.2	YES	CAD	N	+
6	62	M	27744	3	NS	+	25	YES	NO	NL	76	YES	13	N	NPR	YES	160	190	13	YES	N	N	+
7	53	M	8453	1	NS	+	7	NO	YES	NL	80	NO	1	N	BR	NO	154	206	8.6	YES	N	N	-
8	58	M	23749	3	NS	+	21	NO	NI	34.5	70	YES	10	N	BR	YES	168	204	13	YES	N	N	+
9	49	M	8442	1	NS	-	12	YES	YES	NL	78	YES	5	N	NL	YES	125	170	7.2	YES	N	N	+
10	74	M	28394	2	SHT	+	18	NO	YES	NL	86	YES	6	AS	NL	YES	136	204	6.9	YES	N	N	+
11	63	M	7453	1	SHT	+	7	YES	NO	NL	74	YES	8	N	BR	YES	158	324	8.2	YES	N	N	+
12	62	F	29839	1	NS	+	14	NO	NO	NL	80	NO	1	N	NL	NO	146	216	6.6	NO	N	N	-
13	40	M	3245	3	NS	-	19	YES	YES	28.6	86	YES	13	N	NPR	YES	175	178	9.5	YES	CAD	N	+
14	52	M	678	1	NS	-	6	NO	NO	NL	84	NO	2	N	NL	NO	233	168	8.7	YES	N	N	-
15	43	M	14789	1	NS	+	18	YES	YES	NL	90	YES	7	N	BR	YES	136	180	6.4	YES	N	N	+
16	63	M	9744	2	SHT	+	23	NO	NO	32.9	84	YES	8	N	BR	YES	148	186	12	YES	N	N	+
17	42	M	45566	1	SHT	-	21	YES	YES	NL	86	YES	2	N	BR	YES	154	176	11	YES	N	N	+
18	64	M	23747	1	NS	+	11	NO	YES	NL	96	YES	6	N	NL	YES	128	190	6.3	YES	N	N	+
19	38	F	8887	1	NS	-	13	NO	NO	NL	76	NO	2	N	NPR	NO	148	204	7.2	NO	N	N	-
20	40	M	9433	1	NS	+	16	YES	YES	NL	78	NO	4	N	NPR	YES	152	216	7.1	YES	N	N	+
21	36	F	7920	1	NS	+	7	NO	NO	NL	72	NO	3	N	NL	NO	204	358	6.9	YES	N	N	-
22	62	M	67889	1	NS	-	6	YES	YES	NL	68	NO	2	N	NL	NO	190	186	7.9	YES	N	N	-
23	53	M	2847	1	SHT	-	13	YES	NO	NL	70	YES	8	N	NL	YES	176	176	8.9	YES	N	N	+
24	70	M	71234	1	NS	+	14	NO	YES	NL	68	NO	4	N	NL	NO	186	190	7.3	NO	N	N	-
25	42	M	63821	1	NS	-	7	YES	YES	NL	72	NO	3	N	BR	NO	175	170	7.2	YES	N	N	-

SL NO	AGE	SEX	IP NO	SYMPTOM SCORE	PAST HISTORY	FAMILY HISTORY	DURATION OF DIABETES	SMOKING	ALCOHOLISM	BMI	PULSE RATE	SYSTEMIC HYPERTENSION	CLINICAL (DNE) SCORES	CVS	FUNDUS	MICRO ALBUMINURIA	FBS	PPBS	HBA1C	TOTAL CHOLESTEROL >200mg/dl	ECG	CHEST XRAY	NERVE CONDUCTION STUDY
26	42	F	7839	1	NS	+	9	NO	NO	NL	76	NO	2	N	NL	NO	233	260	8.2	YES	N	N	+
27	61	M	7364	1	SHT	+	8	NO	NO	NL	84	YES	6	N	NL	NO	136	190	9.5	NO	LVH	N	+
28	50	M	7942	2	NS	+	19	YES	NO	NL	86	NO	9	N	BR	YES	148	206	9.5	YES	N	N	+
29	38	M	48289	2	NS	-	20	NO	NO	NL	74	YES	12	N	NPR	YES	154	204	6.9	YES		N	+
30	39	F	66879	1	NS	+	7	NO	NO	NL	80	NO	2	N	NL	NO	128	210	6.7	YES	N	N	-
31	48	M	56726	3	SHT	+	20	YES	NO	27.7	86	YES	16	N	PR	YES	186	178	9.9	YES	CAD	N	+
32	48	M	1388	1	NS	+	6	NO	YES	NL	84	NO	2	N	NL	NO	136	180	6.6	YES	N	N	-
33	62	F	3744	2	NS	-	8	NO	NO	NL	72	NO	10	N	NL	NO	240	324	9.3	YES	N	N	+
34	59	M	8893	1	SHT	+	7	YES	NO	NL	88	YES	4	N	BR	YES	136	158	7.3	YES	N	N	+
35	41	M	29848	1	NS	+	6	NO	YES	NL	68	NO	1	N	NL	NO	236	360	6.4	YES	N	N	-
36	47	M	14589	3	SHT	-	13	NO	NO	25.8	68	YES	10	N	PR	YES	158	196	9	YES	N	N	+
37	68	M	546	1	NS	-	19	YES	NO	NL	72	NO	2	N	NL	NO	146	204	7.5	YES	N	N	-
38	38	F	46821	1	NS	+	6	NO	NO	NL	76	NO	2	N	NL	NO	175	210	6.3	YES	N	N	-
39	60	M	9848	1	NS	+	15	NO	YES	NL	84	NO	9	N	NL	NO	138	178	10	NO	N	N	+
40	36	M	23466	1	NS	+	10	YES	NO	NL	86	NO	2	N	NL	NO	291	180	6.1	YES	N	N	-
41	60	F	36787	2	NS	-	7	YES	NO	NL	74	NO	9	N	NL	NO	185	206	8.1	NO	N	N	+
42	58	M	8756	1	NS	+	6	NO	NO	NL	78	NO	1	N	NL	NO	180	188	7.2	YES	N	N	-
43	72	M	7632	1	NS	+	7	YES	YES	NL	76	NO	2	AS	NL	NO	204	180	7.7	YES	N	N	-
44	42	F	64233	4	SHT	+	8	NO	NO	NL	80	NO	10	N	NL	YES	235	310	9.5	YES	N	N	+
45	40	M	8764	1	SHT	-	14	NO	NO	26.3	70	YES	3	N	NPR	YES	176	196	9	YES	N	N	-
46	68	F	4568	4	NS	+	6	NO	NO	NL	78	NO	11	AS	NL	NO	142	170	9.3	NO	N	N	+
47	47	M	46787	1	SHT	-	12	YES	YES	NL	86	YES	4	N	NL	YES	146	168	9.1	NO	LVH	N	+
48	43	M	5688	1	NS	+	6	NO	NO	28.9	74	YES	1	N	NL	YES	140	184	10	YES	N	N	+
49	39	M	23667	4	SHT	+	21	YES	YES	26.2	80	YES	14	N	BR	YES	168	198	9.2	YES	N	N	+
50	48	F	34566	1	NS	+	12	NO	NO	NL	76	NO	2	N	PR	NO	246	310	6.2	NO	N	N	-

CONSENT FORM

Yourself Mr/Mrs/Ms _____ are being asked to be a participant in the study titled – "EVALUATION OF PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH OTHER MICROVASCULAR COMPLICATIONS by Dr Neetha Balaram, Post Graduate student, Department of General Medicine,Coimbatore Medical College. You are eligible after looking into inclusion criteria. You can ask any questions you may have before agreeing to participate.

Purpose of the research

- To evaluate peripheral neuropathy in type 2 diabetes patients by clinical examination and electrophysiologicaly by nerve conduction study and thus do a comparitive analysis.
- To study the correlation of diabetic peripheral neuropathy with age,sex,duration of diabetes,body mass index,hypertension and hypercholestrolemia
- To study the correlation of diabetic peripheral neuropathy with other microvascular complications by assessing microalbuminuria and retinopathy

Procedures involved

This research is intended to study type 2 diabetes mellitus patients for evaluation of peripheral neuropathy by clinical examination and by

nerve conduction study and to correlate with other microvascular complications and risk factors.

Decline from participation

You have the option to decline from participation in the study without any discrimination and you will be treated as per the existing protocol for your condition.

Privacy and confidentiality

Privacy of individual will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization publish results

Results of the study may be published for scientific purposes and / or presented to scientific groups; however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me and I may ask questions at any time.

_____ _____

Signature of Left Hand thumb Impression (Volunteer Subject) Date

_____ _____

Signature (Witness) Date

ABBREVIATIONS

HbAIC	-	Glycosylated Hemoglobin
DIP	-	Distal Interphalangeal Joint
DNE	-	Diabetic Neuropathic Examination
Hz	-	Hertz
CMAP	-	Compound Muscle Action Potential
NCS	-	Nerve Conduction Study
BMI	-	Body Mass Index
MODY	-	Maturity Onset Diabetes Of The Young
DM	-	Diabetes Mellitus
ATP	-	Adenosine Triphosphate
AGE	-	Advanced Glycation Endproducts
DSPN	-	Diabetic Symmetrical Polyneuropathy
DAN	-	Diabetic Autonomic Neuropathy
NADH	-	Nicotinamide Adenine Dinucleotide
NADPH	-	Nicotinamide Adenine Dinucleotide Phosphate
ESRD	-	End Stage Renal Disease
FBS	-	Fasting Blood Sugar
PPBS	-	Post Prandial Blood Sugar